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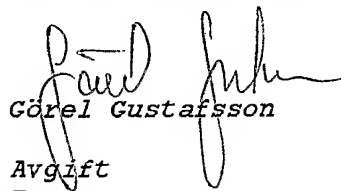
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METHODS

Field of the Invention

This invention relates to methods of screening for modulators of the CLCA family of calcium-activated chloride channels, and to methods of modelling or designing such modulators. These modulators may be used as pharmaceutical agents to treat various diseases.

Background of the Invention

The CLCA family of calcium-activated chloride channels is also known as the CACC family. This family of proteins mediate a Ca^{2+} -activated Cl^- conductance in a variety of tissues in a variety of species. The following family members have been cloned:

- one porcine protein: pCLCA1
- two bovine proteins: bCLCA1, bCLCA2 (also known as Lu-ECAM-1);
- five murine proteins: mCLCA1, mCLCA2, mCLCA3 (also known as gob-5), mCLCA4, mCLCA5
- four human proteins: hCLCA1 (also known as ICACC1 or hCACC1), hCLCA2 (also known as hCACC3), hCLCA3, hCLCA4 (also known as hCACC2)
- two rat proteins: rCLCA1, rCLCA.

The full-length sequences of these CLCA proteins are available from the literature and/or from publicly available sequence databases, as shown below. Where a sequence database identifier is quoted, the world wide web (www) or internet address of the relevant sequence database is as follows: TREMBL (<http://us.expasy.org/sprot/>); SwissProt (<http://us.expasy.org/sprot/>); NCBI Genbank database (<http://www.ncbi.nlm.nih.gov/>).

- *Sus scrofa* (porcine) pCLCA1 protein: Gaspar KJ *et al*, *Physiol. Genomics* (Online), 2000, 3:101-111; TREMBL:Q9TUB5.

- *Bos taurus* (bovine) protein bCLCA1: Cunningham SA *et al*, J Biol Chem, 1995, 270:31016-31026; SWISSPROT:ECLC_BOVIN.
- *Bos taurus* (bovine) protein bCLCA2: Zhu DZ *et al*, Proc Natl Acad Sci USA, 1991, 88(21):9568-7.; database identifier TREMBL:O18744.
- 5 • *Mus musculus* (murine) protein mCLCA1: TREMBL:Q8C324
- *Mus musculus* (murine) protein mCLCA2: TREMBL:Q8C9E1
- *Mus musculus* (murine) protein mCLCA3: Komiya T *et al*, Biochem Biophys Res Commun, 1999, 255:347-351; TREMBL:Q8R049.
- *Mus musculus* (murine) protein mCLCA4: TREMBL:Q91ZF5.
- 10 • *Mus musculus* (murine) protein mCLCA5: TREMBL:Q8BG22.
- *Homo sapiens* (human) protein CLCA1: Agnel M *et al*, FEBS Lett, 1999 Jul, 455(3): 295-301; Gruber AD *et al*, Genomics, 1998, 54:200-214; TREMBL:O95151.
- *Homo sapiens* (human) protein CLCA2: Gruber AD *et al*, Am J Physiol, 1999, 276:C1261-C1270; Agnel M *et al*, FEBS Lett, 1999 Jul, 455(3): 295-301; TREMBL:Q9UNF7.
- 15 • *Homo sapiens* (human) protein CLCA3: Gruber AD *et al*, Biochim Biophys Acta, 1999, 1444:418-423; TREMBL:Q9Y6N3.
- *Homo sapiens* (human) protein CLCA4: Agnel M *et al*, FEBS Lett, 1999 Jul, 455(3): 295-301; TREMBL:Q9UQC9.
- 20 • *Rattus norvegicus* (rat) protein rCLCA1: WO2003037927; NCBI:XP_217689.2.
- *Rattus norvegicus* (rat) protein rCLCA: TREMBL:BAD01114.

25 In addition to the two rat CLCA proteins that have been isolated and sequenced, the following five CLCA protein sequences have been predicted from rat genomic sequences:

- a CLCA protein located between residues 1 and 833 of the sequence NCBI:XP_217688.1 (NCBI Genbank database), hereinafter referred to as rCLCA3.

- a CLCA protein located between residues 851 and 1776 of the sequence NCBI:XP_217688.1 (NCBI Genbank database), hereinafter referred to as rCLCA4.
- a CLCA protein located between residues 3691 and 4637 of the sequence NCBI:XP_217688.1 (NCBI Genbank database), hereinafter referred to as rCLCA5.
- 5 • a CLCA protein hereinafter referred to as rCLCA6: NCBI:XP_217690.2 (NCBI Genbank database).
- a CLCA protein hereinafter referred to as rCLCA7: NCBI:XP_342357.1 (NCBI Genbank database).

10 Equivalent CLCA proteins have been identified in other species, including the tunicate *Ciona intestinalis*, two fish species and two frog species. Some of these proteins have not been fully sequenced, others are proteins predicted from genomic sequences. It is believed that equivalent CLCA proteins exist in all vertebrates (including mammals).

15 For example, the following six sequences are predicted full-length sequences of CLCA proteins in the tunicate *Ciona intestinalis* (translated from the known sequences of CLCA genes). The sequences are listed in the DOE Ciona (ci) database (<http://genome.jgi-psf.org/ciona4/ciona4.home.html>) under the sequence identifiers: ci0100131812, ci0100132657, ci0100137033, ci0100140780, ci0100141485, ci0100148238.

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All the CLCA protein and nucleic acid sequences cited above are incorporated herein by reference.

25 The best characterised CLCA family member is bCLCA2. Important structural motifs have been identified in the protein, such as the symmetrical spacing of five cysteine residues in the N-terminal domain which may be involved in disulphide bonds or a motif that could be involved in binding of metal ions (Zn). Other motifs are sites for N-linked glycosylation as well as sites for Ca²⁺/calmodulin kinase II.

All known human CLCA genes are clustered on the short arm of chromosome 1. Except for hCLCA3, which is a truncated and secreted protein, the other human proteins are synthesized as 125 kD precursor transmembrane proteins that are rapidly cleaved to 90 and 35 kD subunits. The 90 kD subunit is believed to be anchored in the plasma membrane via four transmembrane domains. It has been suggested that the 35 kD subunit may be associated with the 90 kD subunit on the outside of the cell membrane.

Two alternative sets of locations of transmembrane regions in CLCA have been proposed on the basis of experiment and simple computational analysis. The presence of a von Willebrand factor type A (VWA) domain in CLCA proteins has been noted by Whittaker and Hynes, MBC, 2002, 13:3369-3387. The von Willebrand factor type A domain is an ubiquitous extracellular protein domain known to be involved in cell adhesion, in extracellular matrix proteins, and in integrin receptors. It is present in more than 500 different proteins. The role of VWA domain in CLCA is currently not clear, but may be related to scaffolding and/or oligomerization of the CLCA molecule and also modulation of channel activity by binding other proteins.

The three dimensional structures of CLCA proteins are not known. No three dimensional structure has been determined experimentally for any CLCA protein. Also, no complete three dimensional structure has been predicted for any CLCA protein.

It is generally believed that CLCA proteins are calcium-activated chloride channels, and there is much evidence to support this role. However it has also been suggested that the CLCA proteins may be modulating proteins that affect the activity of the actual ion channel (another protein).

Each CLCA family member has a distinct, but sometimes overlapping, tissue expression pattern. hCLCA1, hCLCA4, mCLCA1 and mCLCA3 are expressed in intestinal epithelia. hCLCA3, hCLCA2 and mCLCA1 are expressed in respiratory epithelia. hCLCA1, hCLCA4 and mCLCA1 are expressed in uterus, prostate, epididymis and testes. hCLCA1,

hCLCA2 and mCLCA1 are expressed in the kidney. hCLCA2, mCLCA1 and mCLCA2 are expressed in mammary epithelium, and hCLCA4 is expressed in the brain.

In the airways, hCLCA2, the truncated hCLCA3 and hCLCA4 are expressed under normal conditions. hCLCA1 is normally expressed mainly in the intestine, but also in uterus, prostate, epididymis, testis and kidney and not in the lung or airways. However, recent data from both murine animal models and human airway biopsies obtained from asthma and COPD patients demonstrates upregulation of hCLCA1 in the inflamed airway.

Heterologous expression of hCLCA1, hCLCA2 and mCLCA1 in HEK293 cells is associated with a calcium-sensitive chloride conductance. It has been shown that the CLCA proteins are activated by addition of the Ca^{2+} ionophore ionomycin under patch clamp conditions. The current generated can be inhibited by classic chloride channel blockers such as DIDS, tamoxifen and niflumic acid. It has also been shown that IP_4 , a metabolite of the phospholipase C cascade which accumulates in cells after α -adrenergic or cholinergic stimulation, is a potent inhibitor of calcium-mediated chloride secretion in T84 cells and pancreatic duct cells from cystic fibrosis patients. This molecule might be responsible for the transitory nature of Ca^{2+} -induced secretory responses in epithelial tissues.

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In addition to their anion channel properties, certain CLCA family members seem to serve as cell-adhesion molecules having a role in tumour metastasis and in one case (hCLCA2) a tumor suppressive effect of the protein has been suggested.

The hCLCA1 chloride channel has been suggested as a new therapeutic target, regulating abnormal mucus production and mucosal inflammation. This new therapeutic target is potentially associated with the pathogenesis of a variety of nasal, sinus, and other respiratory disorders including cystic fibrosis, chronic bronchitis, allergic rhinitis, asthma, chronic sinusitis, and COPD (chronic obstructive pulmonary disease). It is also potentially associated with the pathogenesis of a variety of gastrointestinal disorders.

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The international patent application published as WO99/44620 describes hCLCA1 as a therapeutic target in IL-9 mediated development of atopic allergy, asthma-related disorders and cystic fibrosis. It also describes methods for identifying inhibitors of the hCLCA1 gene and its products and the use of such inhibitors to treat those disorders. Inhibitors of hCLCA1 were defined as compounds that down-regulate the chloride channel function of hCLCA1 or the expression of hCLCA1. One particular method of screening for hCLCA1 inhibitors was a competitive binding assay with natural ligands of hCLCA1. Another method involved *in vitro* primary lung cultures that produce secreted eotaxin protein upon IL-9 stimulation. It was suggested that treatment with hCLCA1 inhibitors would result in suppression of IL-9 induced eotaxin response. The application also describes the production of antibodies that specifically bind to hCLCA1 or certain fragments of hCLCA1. Such antibodies may be used to quantify hCLCA1 or may be used as inhibitors by blocking hCLCA1 chloride channel activity through binding to extracellular regions of the protein required for ligand binding or activation.

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The US patent application published as US2003059434 describes a method of treating a subject having a disease state associated with a mucus secretion disorder of the gastrointestinal tract comprising administering to the subject an effective amount of a chloride channel modulator. In particular, this application describes treating diseases such as inflammatory bowel syndrome, ulcerative colitis and Crohn syndrome with a modulator of the hCLCA1 chloride channel. The application describes a method of screening for a compound that modulates hCLCA1 activity by contacting hCLCA1 or a fragment thereof with the compound and detecting modulation of hCLCA1 activity. Whether a given agent acts as an hCLCA1 modulator can be determined by the following methods:

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- by functional assays of the hCLCA1 polypeptide, to determine whether its activity as a calcium activated chloride channel is modulated;
- by direct measurement of the binding or interaction of the compound with hCLCA1 (including competitive binding assays);
- by immunological assays (for example, using an antibody specific for a CLCA1 protein to determine whether protein levels of CLCA1 are affected);
- by assays to determine whether gene expression of the CLCA1 is affected;

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- by assays for mucus production by a mucus-producing cell of the gastrointestinal tract.

Active proteins, such as enzymes, involved in physiological and pathological processes are important targets in the development of pharmaceutical compounds and treatments. Knowledge of the three dimensional (tertiary) structure of active proteins allows the rational design of modulators of such proteins. By searching structural databases of compounds using structural parameters derived from the active protein of interest, it is possible to select compound structures that may interact with these parameters. It is then possible to synthesise the selected compound and test its activity. Alternatively, the structural parameters derived from the active protein of interest may be used to design and synthesise a modulator with the desired activity. Such modulators may be useful as therapeutic agents for treating certain diseases. For example, WO98/07835 discloses crystal structures of a protein tyrosine kinase optionally complexed with one or more compounds. The atomic coordinates of the enzyme structures and any of the bound compounds are used to determine the three dimensional structures of kinases with unknown structure and to identify modulators of kinase functions. As another example, WO99/01476 discloses the crystal structures of anti-Factor IX Fab fragments (antibodies) and their use to identify and design new anticoagulant agents.

20

The practice of the present invention will employ, unless otherwise indicated, conventional methods of virology, immunology, microbiology, molecular biology and recombinant DNA techniques within the skill of the art. Such techniques are explained fully in the literature. See for example: Sambrook *et al.* eds., Molecular Cloning: A Laboratory Manual (3rd ed.) Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY (2001); Ausubel *et al.*, eds., Current Protocols in Molecular Biology, John Wiley & Sons, New York, NY (2002); Glover & Hames, eds., DNA Cloning 3: A Practical Approach, Vols. I, II, & III, IRL Press, Oxford (1995); Colowick & Kaplan, eds., Methods in Enzymology, Academic Press; Weir *et al.*, eds., Handbook of Experimental Immunology, 5th ed., Blackwell Scientific Publications, Ltd., Edinburgh, (1997); Fields, Knipe, & Howley, eds.,

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Fields Virology (3rd ed.) Vols. I & II, Lippincott Williams & Wilkins Pubs. (1996); Flint, *et al.*, eds., Principles of Virology: Molecular Biology, Pathogenesis, and Control, ASM Press, (1999); Coligan *et al.*, eds., Current Protocols in Immunology, John Wiley & Sons, New York, NY (2002).

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The practice of the present invention will employ, unless otherwise indicated, conventional methods of molecular modelling. These methods include Sybyl, Maestro, GOLD, Ludi, LeapFrog and Macromodel computer programs with algorithms and modules therein, as well as other 3D-modelling techniques and tools known to those skilled in the art. Such 3D-modelling techniques were reviewed by Lyne PD in Drug Discov Today (2002), 7:1047-55.

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Summary of the Invention

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We have now identified a metal-dependent hydrolase domain in the CLCA family of calcium-activated chloride channels. It was not previously known that CLCA family members possess a hydrolase domain or hydrolase activity.

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The hydrolase activity of each CLCA protein is believed to be important, whether the CLCA protein is itself a calcium-activated chloride channel or whether it is a modulating protein acting on an ion channel. The hydrolase domain may be a domain of an ion channel modulating its own activity, or, alternatively, it may be a domain of a modulating protein acting on a distinct ion channel. It is believed that modulation of the hydrolase activity of a CLCA protein will result in modulation of the associated calcium-activated chloride channel activity. For any particular CLCA protein, increased hydrolase activity may correlate with increased chloride channel activity or increased hydrolase activity may correlate with decreased chloride channel activity. For example, for hCLCA1 it is likely that increased hydrolase activity correlates with increased chloride channel activity.

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A hydrolase domain is present in the human CLCA family and in the homologous CLCA families of mouse and rat. It is believed that CLCA proteins including the hydrolase domain will be present in every vertebrate species, including all mammals. Mouse, rat,

guinea pig, hamster, dog and monkey are commonly used as model organisms when testing or developing pharmaceutical agents for use in humans.

We identified the hydrolase domain by complex bioinformatics analysis of known CLCA proteins, and subsequently validated existence of the hydrolase domain by structural modelling. We have cloned and expressed an hCLCA1 hydrolase domain protein.

Knowledge of the novel hydrolase domain is useful for diagnostic and therapeutic applications, as explained below.

10

We now provide alternative and improved screening methods for identifying compounds that modulate the activity of a CLCA protein. Such screening methods involve assaying the hydrolase activity of the CLCA protein. Previously known screening methods using functional assays have focussed on measurement of the CLCA chloride channel activity. A disadvantage of the known screening methods is that most anions, including chloride (Cl^-), are difficult to track. There are emerging methods based on fluorescent ion probes or atomic absorption, but these mainly apply to cations like Ca^{2+} , Na^+ and K^+ . Another disadvantage of the known screening methods is that chloride channel activity can only be measured in whole-cell systems, which increases the complexity of primary screening to identify potential CLCA modulators. Thus the full exploitation of ion channels as a class of molecular drug targets is hampered by the lack of efficient screening technology. Screening for modulators of the hydrolase activity is advantageous because it does not require primary screen whole cell methodology. The complexity of the assays used in the primary screen is thus minimised. A biochemical enzyme assay allows the use of screening formats that are simple, robust and amenable to high throughput compound testing.

We further provide methods to design small molecule compounds that may interact with the hydrolase domain of a CLCA protein and thus may modulate the hydrolase activity of the CLCA protein. The small molecules are evaluated and optimized by computer

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modelling of covalent or non-covalent interactions between the small molecules and the CLCA hydrolase domain model. Specific protease modulators targeted at the hydrolase activity of the CLCA protein should be easier to design than specific ion channel modulators. In other words, it should be possible to obtain a better compound faster when
5 targeting a hydrolase as compared to targeting an ion channel directly.

Modulators of CLCA hydrolase activity may be useful as therapeutic agents to treat a variety of diseases.

10 As defined herein, modulation includes any effect on the hydrolase activity of a CLCA protein. Thus modulation may include, for example, any one or more of the following: conformational change, covalent modification, activation, inhibition. Modulators include activators (such as agonists) and inhibitors (such as antagonists). Modulation may be achieved, for example, by increasing or decreasing enzyme activity *per se* or by increasing
15 or decreasing the interaction of the CLCA protein with accessory proteins. Modulation of a CLCA protein by a compound may be brought about, for example, through compound binding to the CLCA protein.

CLCA proteins are potential targets for therapeutic intervention in various diseases. It is
20 possible to devise screening methods to identify compounds (chemical or biological) that modulate the hydrolase activity of a CLCA protein (preferably a human CLCA protein, and most preferably hCLCA1). Such compounds (modulators) include, for example, chemical or hormonal therapeutic agents that modulate the protein. Such compounds may prove useful as therapeutic agents in treating various diseases or disorders in humans
25 and/or other animals. In particular, such compounds may prove useful as therapeutic agents in treating any disease or condition in which the increased or decreased hydrolase activity or unregulated hydrolase activity of a CLCA protein is involved.

The screening methods of the invention are useful in determining whether or not test
30 compounds (chemical or biological) may be suitable for use, *inter alia*, in the treatment of gastrointestinal disorders (for example inflammatory bowel syndrome, ulcerative colitis,

Crohn syndrome) or in the treatment of nasal, sinus, and other respiratory diseases or disorders including cystic fibrosis, chronic bronchitis, allergic rhinitis, asthma, chronic sinusitis, and COPD (chronic obstructive pulmonary disease), or in the treatment of cancer. The screening methods of the invention are particularly useful in determining whether or
5 not test compounds (chemical or biological) may be suitable for use in the treatment of respiratory diseases or disorders, particularly asthma or COPD.

Different forms of modulation may be required in the treatment of different diseases. For example, in the treatment of asthma or COPD in humans it may be necessary to inhibit the
10 chloride channel activity of hCLCA1 and this may be achieved by appropriate modulation of hCLCA1 hydrolase activity (most probably by inhibition of hCLCA1 hydrolase activity). As another example, in the treatment of cancer in humans it may be necessary to activate the chloride channel activity of hCLCA2 and this may be achieved by appropriate modulation of hCLCA2 hydrolase activity.

15

It will be appreciated that the terms "treating" and "treatment of", and variations thereon, include therapeutic and prophylactic (preventative) treatment. Such treatment may involve humans or other animals (preferably humans) susceptible to or suffering from the various diseases or disorders.

20

CLCA modulators are preferably administered in suitable pharmaceutical compositions.

25

The invention further provides a method to design and produce new antibodies that bind specifically to the hydrolase domain of a CLCA protein, including antibodies that bind
specifically to substrate binding regions (the active sites) of the hydrolase domain. These antibodies may be useful for diagnostic or for therapeutic purposes. Antibodies to the ligand binding regions of the hydrolase domain may be used for therapeutic modulation of CLCA activity as they block access to the active site for substrates. Using antibodies specific for the hydrolase domain, rather than using any of the known CLCA antibodies, is
30 particularly advantageous in diagnostic methods because it allows detection of the

functionally important protein region. Using antibodies specific for ligand binding regions of the hydrolase domain, rather than using any of the known CLCA antibodies, is particularly advantageous in therapeutic methods because such antibodies directly modulate the functionally important hydrolase activity.

Detailed description of the Invention

In a first aspect of the invention we provide a method for identifying a compound capable of modulating the hydrolase activity of a CLCA protein which method comprises:

- (a) subjecting one or more test compounds to a screen comprising at least one protein selected from the group consisting of: a CLCA protein or a fragment thereof; a homologue of a CLCA protein or a fragment thereof; and
- (b) measuring the hydrolase activity of the CLCA protein or homologue or fragment; and
- (c) comparing the measured hydrolase activity with the hydrolase activity of the CLCA protein or homologue or fragment in the absence of the test compound.

For use in a method of the invention, preferably each CLCA protein is a mammalian CLCA protein, and most preferably each CLCA protein is a human CLCA protein (most particularly hCLCA1).

A CLCA protein has the capability to exhibit hydrolase activity under appropriate conditions. A protein that is a homologue of a CLCA protein, a protein that is a fragment of a CLCA protein, and a protein that is a fragment of a homologue of a CLCA protein are all proteins that retain the capability to exhibit hydrolase activity.

The term "fragment" as used herein refers to a subsequence of the full length sequence that contains at least 60 consecutive amino acids and preferably at least 100 of the CLCA sequence or of a CLCA homologue. Most preferably a fragment refers to a subsequence of the full length sequence that contains, in increasing order of preference, at least 150, 200, 250 consecutive amino acids of the CLCA sequence or of the CLCA homologue. It is

understood that the protein for use in the invention may be both a fragment and a homologue of a CLCA protein.

When a fragment of a CLCA protein or its homologue is used, that fragment encodes the
5 hydrolase domain of the CLCA protein or a fragment thereof. Preferably a fragment encoding the full hydrolase domain is used. In most full-length CLCA proteins, the full hydrolase domain is contained in the region between residues 1 and 350, most usually between residues 1 and 300. The hydrolase active site located between positions corresponding to 156 and 168 in hCLCA1 contains residues that are highly conserved
10 between different CLCA proteins within a single species and between different species. These are the residues corresponding to His156, Glu157, His160, Glu168 in hCLCA1.

A fragment is large enough to contain all the functional and structural motifs necessary for hydrolase activity. For example, a suitable fragment would include the catalytic metal ion
15 site located between residues 156 and 168 of hCLCA1, including residues His156, Glu157, His160, Glu168 (or corresponding residues from other CLCA proteins). A suitable fragment would also include residues of the structural metal ion binding site between residues 115 and 133, including Cys125, Glu127, His133 of hCLCA1 (or corresponding residues from other CLCA proteins). Preferably, a suitable fragment would include the
20 whole region corresponding to residues 50 to 199 of hCLCA1. More preferably, a suitable fragment would also include the cysteine-rich region of the hydrolase domain, and would thus encompass the sequence corresponding to residues 50 to 262 of hCLCA1, or an even larger fragment that would exhibit desired physicochemical properties (such as good solubility).

25 Suitable protein sequences for use in a method of the invention are provided as SEQ ID Nos: 1 to 37 in the Sequence Listing provided herein. These sequences are fragments of a CLCA protein encoding the full hydrolase domain of the protein or fragments thereof.

30 A protein having any one of the following sequences is suitable for use in a screening method of the invention. Each of the following sequences encodes a complete hydrolase domain of a CLCA protein.

SEQ ID NO:1 from *Bos taurus*: corresponds to residues 8 to 309 of full-length bCLCA2; the hydrolase active site is located between residues 155 and 167 of bCLCA2.

SEQ ID NO:12 from *Bos taurus*: corresponds to residues 1 to 308 of full-length bCLCA1; the hydrolase active site is located between residues 155 and 167 of bCLCA1.

5 SEQ ID NO:2 from *Homo sapiens*: corresponds to residues 1 to 306 of full-length hCLCA1; the hydrolase active site is located between residues 156 and 168 of hCLCA1.

SEQ ID NO:37 from *Homo sapiens*: corresponds to residues 40 to 201 of full-length hCLCA1; the hydrolase active site is located between residues 156 and 168 of hCLCA1.

10 SEQ ID NO:3 from *Homo sapiens*: corresponds to residues 1 to 306 of full-length hCLCA2; the hydrolase active site is located between residues 155 and 167 of hCLCA2.

SEQ ID NO:4 from *Homo sapiens*: corresponds to residues 8 to 311 of full-length hCLCA4; the hydrolase active site is located between residues 164 and 176 of hCLCA4.

SEQ ID NO:5 from *Homo sapiens*: corresponds to residues 3 to 261 of full-length hCLCA3; the hydrolase active site is located between residues 155 and 167 of hCLCA3.

15 SEQ ID NO:6 from *Mus musculus*: corresponds to residues 33 to 311 of full-length mCLCA5; the hydrolase active site is located between residues 164 and 176 of mCLCA5.

SEQ ID NO:7 from *Mus musculus*: corresponds to residues 1 to 308 of full-length mCLCA1; the hydrolase active site is located between residues 155 and 167 of mCLCA1.

20 SEQ ID NO:8 from *Mus musculus*: corresponds to residues 1 to 308 of full-length mCLCA2; the hydrolase active site is located between residues 155 and 167 of mCLCA2.

SEQ ID NO:9 from *Mus musculus*: corresponds to residues 1 to 307 of full-length mCLCA3; the hydrolase active site is located between residues 156 and 168 of mCLCA3.

SEQ ID NO:10 from *Mus musculus*: corresponds to residues 1 to 308 of full-length mCLCA4; the hydrolase active site is located between residues 155 and 167 of mCLCA4.

25 SEQ ID NO:11 from *Sus scrofa*: corresponds to residues 1 to 306 of full-length pCLCA1; the hydrolase active site is located between residues 156 and 168 of pCLCA1.

SEQ ID NO:33 from *Rattus Norvegicus*: corresponds to residues 1 – 307 of full-length rCLCA1; the hydrolase active site is located between residues 156 and 168 of rCLCA1.

5 SEQ ID NO:36 from *Rattus norvegicus*: corresponds to residues 1 to 308 of full-length rCLCA (predicted protein sequence); the hydrolase active site is located between residues 155 and 167 of rCLCA.

10 SEQ ID NO:30 from *Rattus Norvegicus*: corresponds to residues 54 to 254 of full-length rCLCA3 (predicted protein sequence, equivalent to residues 54 to 254 of full-length NCBI:XP_217688.1); the hydrolase active site is located between residues 97 and 109 of rCLCA3 (equivalent to residues 97 and 109 of full-length NCBI:XP_217688.1).

SEQ ID NO:31 from *Rattus Norvegicus*: corresponds to residues 1 to 333 of full-length rCLCA4 (predicted protein sequence, equivalent to residues 851 to 1183 of full-length NCBI:XP_217688.1); the hydrolase active site is located between residues 138 and 250 of rCLCA4 (equivalent to residues 988 and 1000 of full-length NCBI:XP_217688.1).

15 SEQ ID NO:32 from *Rattus Norvegicus*: corresponds to residues 1 to 335 of rCLCA5 (predicted protein sequence, equivalent to residues 3691 to 4025 of full-length NCBI:XP_217688.1); the hydrolase active site is located between residues 155 and 167 of rCLCA5 (equivalent to residues 3845 and 3857 of full-length NCBI:XP_217688.1).

20 SEQ ID NO:34 from *Rattus Norvegicus*: corresponds to residues 33 to 311 of full-length rCLCA6 (predicted protein sequence); the hydrolase active site is located between residues 164 and 176 of rCLCA6.

25 SEQ ID NO:35 from *Rattus Norvegicus*: corresponds to residues 2 to 247 of full-length rCLCA7 (predicted protein sequence); the hydrolase active site is located between residues 156 and 168 of rCLCA7.

30 SEQ ID NO:13 from *Ciona intestinalis*: corresponds to residues 100 to 346 of full-length ci0100131812 (predicted protein sequence); the hydrolase active site is located between residues 210 and 222 of ci0100131812.

SEQ ID NO:14 from *Ciona intestinalis*: corresponds to residues 1 to 274 of full-length ci0100132657 (predicted protein sequence); the hydrolase active site is located between residues 117 and 129 of ci0100132657.

SEQ ID NO:15 from *Ciona intestinalis*: corresponds to residues 1 to 282 of full-length ci0100137033 (predicted protein sequence); the hydrolase active site is located between residues 131 and 143 of ci0100137033.

SEQ ID NO:16 from *Ciona intestinalis*: corresponds to residues 1 to 286 of full-length ci0100140780 (predicted protein sequence); the hydrolase active site is located between residues 134 and 146 of ci0100140780.

SEQ ID NO:17 from *Ciona intestinalis*: corresponds to residues 1 to 273 of full-length ci0100141485 (predicted protein sequence); the hydrolase active site is located between residues 133 and 145 of ci0100141485.

SEQ ID NO:18 from *Ciona intestinalis*: corresponds to residues 24 to 302 of full-length ci0100148238 (predicted protein sequence); the hydrolase active site is located between residues 159 and 171 of ci0100148238.

A protein having any one of the following sequences is suitable for use in a screening method of the invention. Each of the following sequences encodes a fragment of a hydrolase domain of a CLCA protein. Sequences are translated from cDNA sequences (Expressed Sequence Tag or EST). The publicly available EST databases store nucleic acid sequences which are fragments of the expressed region of a gene. Where a sequence database identifier is quoted, the world wide web (www) or internet address of the relevant EST sequence database is as follows: EMBL Nucleotide database (<http://www.ebi.ac.uk/embl/index.html>).

SEQ ID NO:19 from *Danio rerio* (zebrafish), EMBLEST:AW174117 (sequence annotated as similar to bovine CLCA, Lu-ECAM-1).

SEQ ID NO:20 from *Gallus gallus* (chicken), EMBLEST:BU122641.

SEQ ID NO:21 from *Gallus gallus* (chicken), EMBLNEW:CF249701.

SEQ ID NO:22 from *Salmo salar* (Atlantic salmon), EMBLNEW:CA043044.

SEQ ID NO:23 from *Strongylocentrotus purpuratus* (sea urchin), EMBLNEW:CD296258.

SEQ ID NO:24 from *Strongylocentrotus purpuratus* (sea urchin), EMBLNEW:CD306326.

SEQ ID NO:25 from *Strongylocentrotus purpuratus* (sea urchin),
EMBLNEW:CD308947.

SEQ ID NO:26 from *Xenopus tropicalis* (western clawed frog),
EMBLEST:BQ392061.

5 SEQ ID NO:29 from *Xenopus tropicalis* (western clawed frog),
EMBLEST:AL972392.

SEQ ID NO:27 from *Xenopus laevis* (African clawed frog), EMBLEST:BG018962
(sequence annotated as similar to bovine CLCA, Lu-ECAM-1).

SEQ ID NO:28 from *Xenopus laevis* (African clawed frog), EMBLNEW:CF286706.

10

A homologue of a CLCA protein is any variant or isotype of a CLCA protein (including amino acid sequence variants such as alternative splice forms, SNP variants etc).

Preferably the homologue used is a mammalian homologue. Preferably each homologue is a protein containing an amino acid sequence possessing, in increasing order of preference,
15 at least 40%, 50%, 60%, 70%, 75%, 80%, 85%, 90%, 95%, 97%, 98% and 99% amino acid sequence identity to a CLCA protein. The sequence identity between two sequences can be determined by pair-wise computer alignment analysis, using programs such as, BestFit, Gap or FrameAlign. The preferred alignment tool is BestFit. In practice, when
20 searching for similar/identical sequences to the query search, from within a sequence database, it is generally necessary to perform an initial identification of similar sequences using suitable software such as Blast, Blast2, NCBI Blast2, WashU Blast2, FastA, Fasta3 and PILEUP, and a scoring matrix such as Blosum 62. Such software packages endeavor to closely approximate the "gold-standard" alignment algorithm of Smith-Waterman. Thus, the preferred algorithm for use in assessing similarity, i.e. how two primary polypeptide
25 sequences line up, is Smith-Waterman. Identity refers to direct matches, similarity allows for conservative substitutions.

The CLCA protein(s) used in the screening methods of the invention can be prepared by various techniques known to the person skilled in the art. CLCA can be extracted from
30 biological tissue or biological fluids. RNA transcripts can be used to prepare a protein by

in vitro translation techniques according to known methods (Sambrook *et al. supra*).

Alternatively, the CLCA protein(s) can be synthesised chemically. For example, by the Merryfield technique (*J. Amer. Chem. Soc.* 85:2149-2154, (1968)). Numerous automated polypeptide synthesisers, such as Applied Biosystems 431A Peptide Synthesizer also now exist. Alternatively the CLCA protein(s) are produced from a nucleotide sequence encoding the protein using recombinant expression technology. A variety of expression vector/host systems may be used to express the CLCA coding sequences. These include, but are not limited to microorganisms such as bacteria transformed with plasmids, cosmids or bacteriophage; yeasts transformed with expression vectors; insect cell systems transfected with recombinant baculovirus; plant cell systems transfected with plant virus expression systems, such as cauliflower mosaic virus; or mammalian cell systems transfected with plasmids or transduced with recombinant virus (for example adenovirus); selection of the most appropriate system is a matter of choice. Preferably, the CLCA hydrolase domain protein is expressed in bacterial cells, especially *E. coli*, or in mammalian cells. Mammalian cells provide post-translational modifications to recombinant CLCA protein, which include phosphorylation and glycosylation.

In particular embodiments of a screening method according to the invention, the CLCA protein or homologue or fragment is fused to another peptide or protein sequence to form a fusion protein. In any expression system, the CLCA protein or homologue or a fragment thereof may be expressed as a fusion protein. Such fusion proteins are useful for the detection of expressed protein, facilitating the purification of the protein and/or for increasing the solubility of the protein. When a protein domain or part of a protein is expressed, a fusion protein may increase the solubility and decrease aggregation by interacting with hydrophobic surface-exposed regions of the domain. Examples of such fusion peptides/proteins are poly-histidine, FLAG-, cmc-, strep-, GST-, MBP-, and GFP-tags. The tag may be fused to the N- or C- terminus of the CLCA protein, or incorporated at a certain position between two amino acid residues of the CLCA sequence.

Expression vectors usually include an origin of replication, a promoter, a translation initiation site, optionally a signal peptide, a polyadenylation site, and a transcription termination site. These vectors also usually contain one or more antibiotic resistance

marker gene(s) for selection. As noted above, suitable expression vectors may be plasmids, cosmids or viruses such as phage or retroviruses. The coding sequence of the protein is placed under the control of an appropriate promoter, control elements and transcription terminator so that the nucleic acid sequence encoding the protein is transcribed into RNA in the host cell transformed or transfected by the expression vector construct. The coding sequence may or may not contain a signal peptide or leader sequence for secretion of the protein out of the host cell. Expression and purification of the CLCA protein(s) can be easily performed using methods well known in the art (for example as described in Sambrook *et al. supra*).

The methods according to the invention are screening methods and may be operated using conventional procedures. The test compound or compounds to be screened are brought into contact with the purified or partially purified protein(s), or a cell capable of producing it, or a cell membrane preparation or a cell lysate preparation thereof, and modulation of the protein is determined. The conditions of the screen are suitably selected to allow a binding interaction between an active compound (modulator) and the protein. Cells capable of producing the protein include cells naturally expressing CLCA and cells expressing recombinant CLCA.

The screening method of the invention may comprise an assay system wherein the test compound is brought into contact with the purified or partially purified CLCA protein (or a homologue thereof or a fragment of either), and modulation of the protein (or homologue or fragment) is determined. In particular embodiments, the CLCA protein or homologue or fragment is present as a fusion protein. The modulation is determined by measuring modulation of hydrolase activity of CLCA. Methods to measure hydrolase activity are described in the literature and well-known to those skilled in the art. Methods include but are not limited to the following protease assay formats:

- Fluorescence intensity using fluorogenic quenched FRET peptide/protein substrates;
- Absorbance using chromogenic peptide/protein substrates;

- Radioactive formats like SPA or FlashPlate using radioactively labelled biotinylated peptide/protein substrates;
- Fluorescence polarization, using fluorescence labelled biotinylated peptide substrates;
- 5 • AlphaScreen, using biotinylated and tagged (such 6xHis, FLAG) protein or peptide substrates;
- Label free detection, using LC-MS to demonstrate the cleavage of a peptide/protein substrate;
- Label free detection, using SDS-PAGE to demonstrate cleavage of a protein
- 10 substrate.

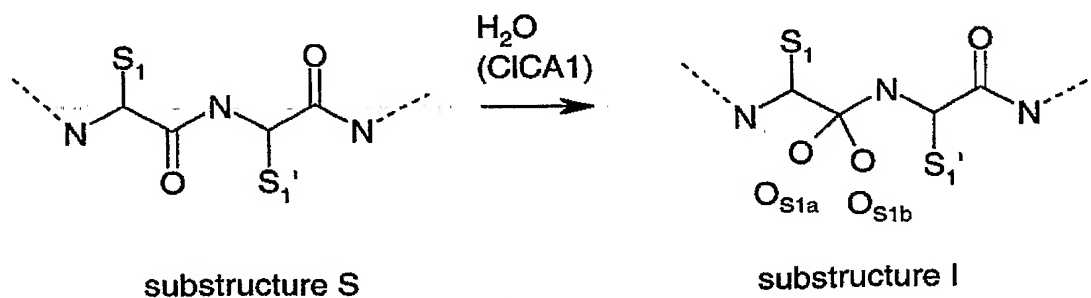
Preferably, hydrolase activity is measured by following the hydrolytic cleavage of a fluorogenic or chromogenic peptide or protein substrate.

To measure the hydrolase activity of a CLCA protein, a suitable protein or peptide

15 substrate must first be selected. The substrate may be selected by following standard procedures well-known in the art, including for example by screening of combinatorial peptide libraries (J. Combin. Chem. 2(5), 461-466, (2000); WO 97/40065), by structure-based design (US2002/0151028), or by combinations thereof resulting in mini-libraries/

20 The structure-based design of substrates is based on the predicted three-dimensional structure of the CLCA hydrolase domain as provided herein and computer molecular modelling methods and an initial di-peptidic substrate model (substructure S in scheme x). The initial di-peptidic substrate is preferably a model where the scissile amide is modelled as the tetrahedral intermediate of a Gly peptide (substructure I in scheme x).

25



Scheme x

Optionally, Gly di, tri, tetra, penta or hexapeptides are used as initial substrate models as their tetrahedral intermediates regarding the scissile bond (J. Biomol. Structure and Dynamics 17(6), 933-946 (2000)). Side-chains, additional amino acid residues,

5 chromophoric or fluorogenic residues can be added, evaluated and optimized by computer modelling of covalent or non-covalent interactions between the substrate or its intermediate and the CLCA hydrolase domain model. Computer modelling methods include, but are not limited to, Sybyl, Maestro, GOLD, Ludi, LeapFrog and Macromodel computer programs with algorithms and modules therein. Interactions that may be
10 evaluated include, but are not limited to, bond stretching, angle bending, rotational and torsional strain, van der Waals forces, solvation energies, electrostatic and dipole-dipole, charge-dipole and hydrogen bond interactions. Preferred interactions between the initial substrate and enzyme models include, but are not limited to, between O_{S1a} (as defined in scheme x) and Glu157 of hCLCA1 (or corresponding glutamate residue in other CLCA
15 homologs) and O_{S1b} and catalytic metal ion in CLCAs. The peptide substrates thus designed and evaluated are then synthesized as libraries by methods well known to the person skilled in the art. These substrate libraries are next screened to select the most preferred substrates for the modulator screening assays of the invention.

20 The screening methods of the invention may comprise an assay system wherein the test compound is brought into contact with a cell capable of producing the CLCA protein (or a homologue thereof or a fragment or either), or with a cell membrane preparation thereof, or with a cell lysate preparation thereof, and modulation of the CLCA protein (or homologue or fragment) is determined. In particular embodiments, the CLCA protein or homologue
25 or fragment is present as a fusion protein. The modulation is determined by measuring modulation of hydrolase activity of CLCA as described above.

As described herein, cells (including mammalian cells, bacterial cells, yeast cells, insect cells etc) can be engineered to express a CLCA protein. The screening methods of the
30 invention may use a cell or cell line expressing genomic DNA or cDNA encoding a CLCA protein or a homologue thereof, or a fragment of either.

Convenient DNA sequences for use in the various aspects of the invention may be obtained using conventional molecular biology procedures, for example by probing a human genomic or cDNA library with one or more labeled oligonucleotide probes containing 10 or more contiguous nucleotides designed using known CLCA nucleotide sequences. Alternatively, pairs of oligonucleotides one of which is homologous to the sense strand and one to the antisense strand, designed using the nucleotide sequences described here to flank a specific region of DNA may be used to amplify that DNA from a cDNA library. Primers or probes may be manufactured using any convenient method of synthesis. Examples of such methods may be found in standard textbooks, for example "Protocols for Oligonucleotides and Analogues; Synthesis and Properties," Methods in Molecular Biology Series; Volume 20; Ed. Sudhir Agrawal, Humana ISBN: 0-89603-247-7 (1993); 1st Edition. If required the primer(s) may be labeled to facilitate detection.

Preferably the genomic DNA or cDNA expressing a CLCA protein is a mammalian sequence, and most preferably a human sequence (particularly hCLCA1).

A homologue of a genomic DNA or cDNA expressing a CLCA protein is any DNA variant that encodes a CLCA protein. Preferably each homologue contains a nucleic acid sequence possessing, in increasing order of preference, at least 60%, 70%, 75%, 80%, 85%, 90%, 95%, 97%, 98% and 99% sequence identity to the genomic DNA or cDNA. A fragment of a genomic DNA or cDNA expressing a CLCA protein, or a fragment of a DNA homologue, is a subsequence of the full length sequence that contains at least 10 consecutive bases of the CLCA DNA sequence or of the CLCA DNA homologue. It is understood that the DNA for use in the invention may be both a fragment and a homologue of a CLCA genomic DNA or cDNA.

Any convenient test compound or library of test compounds may be used in conjunction with the screening methods of the invention. Particular test compounds include low molecular weight chemical compounds (preferably with a molecular weight less than 1500 Daltons) suitable as pharmaceutical or veterinary agents for human or animal use, or

compounds for non-administered use such as cleaning/sterilizing agents or for agricultural use. Test compounds may also be biological in nature, such as hormones or antibodies. As used herein the term antibody includes both monoclonal, polyclonal, humanized and chimeric antibodies and is to be understood to mean a whole antibody or a fragment thereof, a single chain antibody, a multimeric monospecific antibody or fragment thereof, or a bi- or multi-specific antibody or fragment thereof. Each of these types of antibody and derivative are well known to the person skilled in the art. Methods of making and detecting antibodies are well known (Campbell; Monoclonal Antibody Technology, in: Laboratory Techniques in Biochemistry and Molecular Biology, Volume 13. Eds: Burdon R et al. Elsevier, Amsterdam (1984)).

Any compound identified by any screening method of the invention is selected by the screen as a compound capable of modulating the hydrolase activity of a CLCA protein. Such a compound may prove useful, for example, in treating any disease or condition in which the increased or decreased hydrolase activity or unregulated hydrolase activity of a CLCA protein is involved (for example through its effect on the chloride channel activity). In particular, any compound identified by the screening methods of the invention may prove useful in treating gastrointestinal disorders (for example inflammatory bowel syndrome, ulcerative colitis, Crohn syndrome) or in the treatment of nasal, sinus, and other respiratory diseases or disorders including cystic fibrosis, chronic bronchitis, allergic rhinitis, asthma, chronic sinusitis, and COPD (chronic obstructive pulmonary disease) or in the treatment of cancer. Compounds identified by the screening methods of the invention may be particularly useful in treating respiratory diseases or disorders, particularly asthma or COPD. The invention thus extends to a compound identified by a screening method of the invention as defined herein.

In a further aspect of the invention we provide a compound capable of modulating the hydrolase activity of a CLCA protein, or a pharmaceutically acceptable derivative of the compound, wherein said compound is identified by a screening method of the invention.

The compound may modulate CLCA hydrolase activity by activation or by inhibition. A pharmaceutically acceptable derivative includes a pharmaceutically acceptable salt or ester of the compound.

5 In a further aspect, we provide use of the compound according to the invention as a therapeutic agent. Such a therapeutic agent may be useful for the treatment of any one of the diseases or disorders discussed above. In a preferred embodiment, the compound is suitable for use in the treatment of respiratory diseases or disorders, particularly asthma or COPD.

10

In a further aspect of the invention, we provide use of a compound capable of modulating the hydrolase activity of CLCA, or a pharmaceutically acceptable derivative of the compound, in the preparation of a medicament for the treatment of a disease or disorder, wherein said compound is identified by a screening method of the invention.

15

In a further aspect of the invention we provide a pharmaceutical composition comprising a pharmaceutically acceptable carrier and a compound capable of modulating the hydrolase activity of CLCA, or a pharmaceutically acceptable derivative of the compound, wherein said compound is identified by a screening method of the invention.

20

A pharmaceutically acceptable carrier may be an excipient or a diluent.

We also provide a method of preparing a pharmaceutical composition which comprises:

- 25
- i) identifying a compound capable of modulating the hydrolase activity of a CLCA protein, wherein said compound is identified by a screening method of the invention;
 - ii) mixing the compound or a pharmaceutically acceptable derivative thereof with a pharmaceutically acceptable carrier.

30

We provide use of any composition according to the invention as a therapeutic agent.

Such a therapeutic agent may be useful for the treatment of any one of the diseases or disorders discussed above. In a preferred embodiment, the composition is suitable for use in the treatment of respiratory diseases or disorders, particularly asthma or COPD.

5 The compositions of the invention may be in a form suitable for oral use (for example as tablets, lozenges, hard or soft capsules, aqueous or oily suspensions, emulsions, dispersible powders or granules, syrups or elixirs), for topical use (for example as creams, ointments, gels, or aqueous or oily solutions or suspensions), for administration by inhalation (for example as a finely divided powder or a liquid aerosol), for administration by insufflation
10 (for example as a finely divided powder) or for parenteral administration (for example as a sterile aqueous or oily solution for intravenous, subcutaneous, intramuscular or intramuscular dosing or as a suppository for rectal dosing).

The compositions of the invention may be obtained by conventional procedures using
15 conventional pharmaceutical excipients, well known in the art. Thus, compositions intended for oral use may contain, for example, one or more colouring, sweetening, flavouring and/or preservative agents.

Suitable pharmaceutically acceptable excipients for a tablet formulation include, for
20 example, inert diluents such as lactose, sodium carbonate, calcium phosphate or calcium carbonate, granulating and disintegrating agents such as corn starch or algenic acid; binding agents such as starch; lubricating agents such as magnesium stearate, stearic acid or talc; preservative agents such as ethyl or propyl p-hydroxybenzoate, and anti-oxidants, such as ascorbic acid. Tablet formulations may be uncoated or coated either to modify
25 their disintegration and the subsequent absorption of the active ingredient within the gastrointestinal track, or to improve their stability and/or appearance, in either case, using conventional coating agents and procedures well known in the art.

30 Compositions for oral use may be in the form of hard gelatin capsules in which the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules in which the active ingredient is mixed with water or an oil such as peanut oil, liquid paraffin, or olive oil.

Aqueous suspensions generally contain the active ingredient in finely powdered form together with one or more suspending agents, such as sodium carboxymethylcellulose, methylcellulose, hydroxypropylmethylcellulose, sodium alginate, polyvinyl-pyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents such as lecithin or condensation products of an alkylene oxide with fatty acids (for example polyoxyethylene stearate), or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene sorbitan monooleate. The aqueous suspensions may also contain one or more preservatives (such as ethyl or propyl p-hydroxybenzoate), anti-oxidants (such as ascorbic acid), colouring agents, flavouring agents, and/or sweetening agents (such as sucrose, saccharine or aspartame).

Oily suspensions may be formulated by suspending the active ingredient in a vegetable oil (such as arachis oil, olive oil, sesame oil or coconut oil) or in a mineral oil (such as liquid paraffin). The oily suspensions may also contain a thickening agent such as beeswax, hard paraffin or cetyl alcohol. Sweetening agents such as those set out above, and flavouring agents may be added to provide a palatable oral preparation. These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water generally contain the active ingredient together with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients such as sweetening, flavouring and colouring agents, may also be present.

The pharmaceutical compositions of the invention may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil, such as olive oil or arachis oil, or a mineral oil, such as for example liquid paraffin or a mixture of any of these. Suitable emulsifying agents may be, for example, naturally-occurring gums such as gum acacia or gum tragacanth, naturally-occurring phosphatides such as soya bean, lecithin, an esters or partial esters derived from fatty acids and hexitol anhydrides (for example sorbitan monooleate) and condensation products of the said partial esters with ethylene oxide such as polyoxyethylene sorbitan monooleate. The emulsions may also contain sweetening, flavouring and preservative agents.

10

Syrups and elixirs may be formulated with sweetening agents such as glycerol, propylene glycol, sorbitol, aspartame or sucrose, and may also contain a demulcent, preservative, flavouring and/or colouring agent.

15

The pharmaceutical compositions may also be in the form of a sterile injectable aqueous or oily suspension, which may be formulated according to known procedures using one or more of the appropriate dispersing or wetting agents and suspending agents, which have been mentioned above. A sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example a solution in 1,3-butanediol.

20

Suppository formulations may be prepared by mixing the active ingredient with a suitable non-irritating excipient which is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Suitable excipients include, for example, cocoa butter and polyethylene glycols.

25

Topical formulations, such as creams, ointments, gels and aqueous or oily solutions or suspensions, may generally be obtained by formulating an active ingredient with a conventional, topically acceptable, vehicle or diluent using conventional procedure well known in the art.

30

Compositions for administration by insufflation may be in the form of a finely divided powder containing particles of average diameter of, for example, 30 μ or much less, the powder itself comprising either active ingredient alone or diluted with one or more physiologically acceptable carriers such as lactose. The powder for insufflation is then conveniently retained in a capsule containing, for example, 1 to 50 mg of active ingredient for use with a turbo-inhaler device, such as is used for insufflation of the known agent sodium cromoglycate.

Compositions for administration by inhalation may be in the form of a conventional pressurised aerosol arranged to dispense the active ingredient either as an aerosol containing finely divided solid or liquid droplets. Conventional aerosol propellants such as volatile fluorinated hydrocarbons or hydrocarbons may be used and the aerosol device is conveniently arranged to dispense a metered quantity of active ingredient.

For further information on Formulation the reader is referred to Chapter 25.2 in Volume 5 of Comprehensive Medicinal Chemistry (Corwin Hansch; Chairman of Editorial Board), Pergamon Press 1990.

The amount of active ingredient that is combined with one or more excipients to produce a single dosage form will necessarily vary depending upon the host treated and the particular route of administration. For example, a formulation intended for oral administration to humans will generally contain, for example, from 0.5 mg to 2 g of active agent compounded with an appropriate and convenient amount of excipients which may vary from about 5 to about 98 percent by weight of the total composition. Dosage unit forms will generally contain about 1 mg to about 500 mg of an active ingredient. For further information on Routes of Administration and Dosage Regimes the reader is referred to Chapter 25.3 in Volume 5 of Comprehensive Medicinal Chemistry (Corwin Hansch; Chairman of Editorial Board), Pergamon Press 1990.

The size of the dose for therapeutic or prophylactic purposes of a compound will naturally vary according to the nature and severity of the conditions, the age and sex of the animal or patient and the route of administration, according to well known principles of medicine.

In using a compound for therapeutic or prophylactic purposes it will generally be administered so that a daily dose in the range, for example, 0.5 mg to 75 mg per kg body weight is received, given if required in divided doses. In general lower doses will be administered when a parenteral route is employed. Thus, for example, for intravenous administration, a dose in the range, for example, 0.5 mg to 30 mg per kg body weight will generally be used. Similarly, for administration by inhalation, a dose in the range, for example, 0.5 mg to 25 mg per kg body weight will be used. Oral administration is however preferred.

10

In a further aspect of the invention we provide a method for the treatment of a disease or disorder which comprises administering a therapeutically effective amount of a compound or a pharmaceutically acceptable derivative thereof to a human or other animal, wherein the compound has the capability to modulate the hydrolase activity of a CLCA protein and said compound is identified by a screening method of the invention.

15

In a further aspect of the invention we provide a method for the treatment of a disease or disorder which comprises administering a therapeutically effective amount of a pharmaceutical composition to a human or other animal, in which the pharmaceutical composition comprises a pharmaceutically acceptable carrier and a compound capable of modulating the hydrolase activity of CLCA, or a pharmaceutically acceptable derivative of the compound, wherein said compound is identified by a screening method of the invention.

20

According to a further aspect of the invention, we provide methods to design or select chemical modulators of a CLCA protein by using a model of the hydrolase domain structure of a CLCA protein or a homologue thereof or a fragment of either. Small-molecule modulators of a CLCA protein may be designed or selected to fit into the shape of the hydrolase domain region, particularly into the shape of the active site (substrate binding site or cleft).

30

A modulator of CLCA hydrolase activity may be designed by rational design methods based on interaction of a potential modulator with a CLCA hydrolase domain structure. A modulator of CLCA hydrolase activity may be selected by searching a structural database of compounds using parameters derived from the structure of the CLCA hydrolase domain, and selecting a compound structure that may interact with these parameters. It is then possible to synthesise the designed or selected compound and test its ability to modulate CLCA hydrolase activity.

We provide methods to design or select small molecule compounds that may interact with the hydrolase domain of a CLCA protein and thus may modulate the hydrolase activity of the CLCA protein. The small molecules are evaluated and optimized by computer modelling of covalent or non-covalent interactions between the small molecules and the CLCA hydrolase domain model. Interactions that may be evaluated include bond stretching, angle bending, rotational and torsional strain, van der Waals forces, solvation energies, electrostatic and dipole-dipole, charge-dipole, hydrogen bond, and other relevant interactions. Preferred interactions between the small molecules and enzyme models include a functionality capable of coordinating metal ions such as the catalytic metal ion in CLCA proteins. Suitable modelling methods are known to those skilled in the art. For example, for a review of coordinators used for MMP inhibitors, see Inflammation Research (2003), 52(3), 95-100 and Expert Opinion on Therapeutic Patents (2002), 12(5), 665-707.

A full-atom three-dimensional model of the hydrolase domain of a CLCA protein is defined by the set of atomic coordinates shown in Table 1. To obtain these coordinates, the protein fragment encoded by residues 40 to 201 of the hCLCA1 sequence (SEQ ID NO:37) was manually aligned on top of the hMMP-11 structure (PDB code 1hv5) and optimised using standard modules of the Insight II software package (Accelrys Inc.). The resulting model contained the predicted two metal coordinating sequences: 115-133 ('structural Zn-site') and 156-168 ('catalytic Zn-site'). The active site is believed to comprise the amino acid residues within 15Å of atom Zn-1300 in the set of atomic coordinates shown in Table 1 (found after the Examples).

In Table 1, the amino acid sequence of residues 40 to 201 of hCLCA1 (SEQ ID NO:37) is shown in the lines that begin with the code SEQRES followed by the line number (162 amino acid residues in total). In Table 1 the atomic coordinates are listed in those lines that begin with the code ATOM or HETATM, one atom per line. Following the code are:
 5 the unique atom number; the atom name; the amino acid residue name; the amino acid residue number; the atomic coordinates x, y, and z in orthogonal Angstrom space; the atomic occupancy factor (default value for *in silico* molecular model); the calculated electrostatic charge. Amino acids are abbreviated by three letter codes:

	A = ALA = alanine	C = CYS = cysteine	D = ASP = aspartate
10	E = GLU = glutamate	F = PHE = phenylalanine	G = GLY = glycine
	H = HIS = histidine	I = ILE = isoleucine	K = LYS = lysine
	L = LEU = leucine	M = MET = methionine	N = ASN = asparagine
	P = PRO = proline	Q = GLN = glutamine	R = ARG = arginine
	S = SER = serine	T = THR = threonine	V = VAL = valine
15	W = TRP = tryptophan	Y = TYR = tyrosine.	

According to a further aspect of the invention, we provide a method to design a compound capable of modulating CLCA hydrolase activity which comprises molecular modelling based on the interaction of a potential modulator with a hydrolase domain of a CLCA
 20 protein or homologue or fragment of either, wherein the three-dimensional structure of the hydrolase domain is defined by the set of atomic coordinates shown in Table 1.

We further provide a method to design a compound capable of modulating CLCA hydrolase activity which comprises molecular modelling based on the interaction of a
 25 potential modulator with the active site of a hydrolase domain of a CLCA protein or homologue or fragment of either, wherein the three-dimensional structure of the hydrolase domain is defined by the set of atomic coordinates shown in Table 1 and the active site comprises the amino acid residues within 15Å of atom Zn-1300 in the set of atomic coordinates shown in Table 1.

According to a further aspect of the invention, we provide a method for *in silico* screening for a compound capable of modulating CLCA hydrolase activity which comprises

- a) searching a structural database of compounds; and
- b) selecting a compound structure that may interact with a hydrolase domain of a CLCA protein or homologue or fragment of either, wherein the three-dimensional structure of the hydrolase domain is defined by the set of atomic coordinates shown in Table 1.

We further provide a method for *in silico* screening for a compound capable of modulating CLCA hydrolase activity which comprises

- a) searching a structural database of compounds; and
- b) selecting a compound structure that may interact with the active site of a hydrolase domain of a CLCA protein or homologue or fragment of either, wherein the three-dimensional structure of the hydrolase domain is defined by the set of atomic coordinates shown in Table 1 and the active site comprises the amino acid residues within 15Å of atom Zn-1300 in the set of atomic coordinates shown in Table 1.

We further provide uses of therapeutic agents wherein each therapeutic agent is capable of binding to the hydrolase domain of a CLCA protein or homologue thereof or a fragment of either. Preferably the therapeutic agent is selected from the group consisting of: monoclonal antibodies, polyclonal antibodies, humanized antibodies, phage display antibodies, aptamers, constrained peptides, therapeutic peptides, tagged peptides.

Antibodies specifically binding to the hydrolase domain can be designed using the predicted hydrolase domain structure and produced as described below. The predicted three-dimensional structure of the CLCA hydrolase domain can be used to select surface peptide sequences suitable as epitopes for antibody production to enhance the probability of obtaining desired properties of such antibodies. For example, a sequence close to the catalytic cleft (for example hCLCA1 sequences Pro117-Gly129, Trp163-Glu173 and Leu177-Arg186) should inhibit the hydrolase activity for therapeutic use. Another

example is identification of surface sequences with maximal and inter-species homology (human vs rodents, dog) as diagnostic tools or tools useful in the development of modulators to the hydrolase domain. Yet another example is to select surface sequences which include potential glycosylation sites in order to probe the glycosylation state of the full protein, useful for diagnostic purposes and for development of expression methods for protein production. Such sequences are 5 to 25 amino acids in length, preferably 10 to 20, and located in non-helical regions. The most preferred sequences are soluble and slightly hydrophobic, with calculated logP at -2 to 4, preferably 0 to 2. The sequences can preferably attain the same conformation in solution as they present on the protein surface. The conformational preferences of such peptides can be assessed by computational simulation methods such as molecular dynamics. Such simulations are also useful in distinguishing whether the potential epitope peptide should have free charged N,C-termini or be capped. For a review on structure-guided epitope selection, see Protein Science (1994 Oct), 3(10), 1670-86.

According to a further aspect of the invention, we provide a method for designing an antibody capable of modulating the hydrolase activity of a CLCA protein which method comprises using the three-dimensional structure of a CLCA hydrolase domain to identify suitable epitopes in the vicinity of the active site, wherein the three-dimensional structure of the hydrolase domain is defined by the set of atomic coordinates shown in Table 1 and the active site comprises the amino acid residues within 15Å of atom Zn-1300 in the set of atomic coordinates shown in Table 1. In a particular embodiment of this method, the epitopes include only surface residues within 15Å of atom Zn-1300 in the set of atomic coordinates shown in Table 1.

Antibodies specifically binding to the hydrolase domain can be raised by introducing the protein domain itself, peptides thereof or genetic material coding for the hydrolase domain or parts thereof into animals or plants. These organisms can be natural breeds or transgenic. Using known antibody generating techniques, antibodies specific towards the hydrolase domain can be raised. Polyclonal and utilising hybridoma technology also monoclonal antibodies can be produced. Antibodies can also be produced by phage display or ribosomal display technologies. These methods can also be combined with

affinity maturation techniques and techniques for producing recombinant or engineered antibodies. Covalent display is yet another technology which can be used for antibody production. Production of the antibodies will employ, unless otherwise indicated, conventional methods within the skill of the art. Such techniques are explained fully in the literature. See for example: Handbook of Experimental Immunology. Volume 1: Immunochemistry, Ed by D.M.Weir, Blackwell Scientific Publications, 1986, page 8.1 – 8.21; Immunotechnology. Ed by J.P. Gosling and D.J. Reen. Portland Press 1993, page 1 – 11; J. Lipid Research. S.-C. J. Yeung, J. Anderson, K. Kobayashi, K. Oka and L. Chan (1997), 38: 2627 – 2632; J. Immunol. Meth. S.Nagata, G. Salvatore and I. Pastan (2003), 280: 59 – 72; Expert Opin. Biol.Ther. G. Nölke, R. Fisher and S. Schillberg (2003), 3(7): 1153 – 1162; Drug Discovery Today. J. Osburn, L. Jermutus and A. Duncan (2003), 8(18): 845 – 851; Placenta U. Schmitz, A. Versmold, P.Kaufmann and H.-G. Frank (2000), 21 (suppl. A): S106 – S112; J. Immunol. Meth. R.A. Irving, G. Coia, A. Roberts, S.D. Huttall and P.J. Hudson (2001) 248: 31 – 45; Ann. Rev. Biomed. Eng. J. Maynard and G. Georgiou (2000) 02: 339 – 376; BioTechniques J.V. Gavilondo and J.W. Larrick (2000), 29(1):128 – 145.

The present invention will now be described with reference to the following non-limiting Examples.

EXAMPLE 1

Expression and characterisation of an hCLCA1 hydrolase domain protein

The predicted 3-dimensional structure of the hCLCA1 hydrolase domain was used to determine suitable start and end residues of protein fragments that would be expressed as soluble and stable proteins. The sequence close to the N-terminus (Gln52-Met56) threads under a loop (Lys86-Leu105) where a free amino terminus is likely to induce instability. Since the preceding seq. Glu45-Gln51 is predicted to comprise a β -sheet starting with a Pro-x-x-Pro turn, a position preceding the first proline was judged to be a suitable N-

terminus for expression. Close to the C-terminus, there is a hydrophobic surface patch that could potentially affect solubility and aggregation. It is therefore advantageous to include an additional 60-100 residues of unpredicted structure, denoted 'the Cys-rich region' in the bioinformatics analysis, to occlude the predicted hydrophobic surface. Also, the sequence
5 of the 'Cys-rich region' is highly conserved in CLCA variants from different species, which indicates it being part of the hydrolase domain.

Five constructs were made, encoding the following residues of full-length hCLCA1 protein: 50 to 199, 23 to 199, 23 to 63, 45 to 199 and 45 to 263.

10 The hCLCA1 sequence encoding residues 50-199, 23-199, 23-263, 45-199 and 45-263 was PCR amplified.

Primers for the 50-199 construct were as follows:

ATGTCGACCATATGATTCAACAAATAAAGGA (SEQ ID NO:38) and
15 ATGCGGCCGCTCACTTCTTTACTACATTTGTAC (SEQ ID NO:39).

Primers for the other constructs were

5' primer for start at residue 23: CATATGTCACTCATTTCAGCTGAACAAC (SEQ ID NO:40),

5' primer for start at residue 45: CATATGGAAGATGAAACACTCATTC (SEQ ID
20 NO:41),

3' primer for stop at residue 199: GCGGCCGCTCACTTCTTTACTACATTTGTACC (SEQ ID NO:42),

3' primer for stop at residue 263: GCGGCCGCTCACTTGTTTGGAGCTTCTTTG (SEQ ID NO:43).

25 The sequences of the above primers are included in the Sequence Listing provided herein.

A plasmid containing the full length hCLCA1 sequence was used as template. The PCR fragments were cloned into TA vectors, the correct sequences were verified and the fragments were subcloned into an *E. coli* expression vector, and inserted into an expression

host strain. The proteins were expressed as insoluble inclusion bodies by growing the *E. coli* expression strain to an OD₆₀₀ of 3-4 and inducing with IPTG for 4-5 h. The cells were harvested, lysed, and the insoluble part of the lysate was separated by centrifugation. The pellets containing the inclusion bodies were solubilised in urea and refolded by a gradual lowering of urea concentration using dialysis. SDS-PAGE of the refolded protein comprising residues 50-199 confirmed the presence of soluble protein of the expected molecular weight 17 kDa. The identity and correct N-terminus of the protein was verified by N-terminal sequencing.

Each of the five hCLCA1 constructs expressed a protein that refolded which indicated that each construct encoded a structural domain of the hCLCA1 protein.

EXAMPLE 2

Assaying hydrolase activity of hCLCA1 protein and screening for modulators

An *in vitro* hydrolase assay is used to measure the activity of the refolded hCLCA1 protein fragment produced by the method described in Example 1.

The hydrolase assay measures the hydrolytic cleavage of fluorogenic peptide substrates. Suitable peptide substrates are first identified by design and screening of peptide libraries.

The hydrolase assay is performed in white 384-well plates with each well containing 100 mM Tris-HCl (pH 7.5), 100 mM NaCl, 20 mM CaCl₂, 20 μ M ZnCl₂, 0.05% Brij 35, 50 μ M fluorogenic substrate and 100 ng of hCLCA1 in a total volume of 80 μ l. The assay plates are incubated at room temperature followed by reading in a Tecan Safire at the required time intervals to obtain rates of reaction.

When screening for modulators of hCLCA1 hydrolase activity, the potential modulators are added to dry wells in 1 μ l of DMSO giving a final DMSO concentration of 1.25% in the hydrolase assay.

EXAMPLE 3**Assaying hydrolase activity of hCLCA1 protein and screening for modulators**

The purified hCLCA1 hydrolase domain (50 ng/ml final concentration) is incubated for 30 minutes at RT in assay buffer (0.1M Tris-HCl, pH 7.3 containing 0.1M NaCl, 20mM CaCl₂, 0.040 mM ZnCl and 0.05% (w/v) Brij 35) in the presence or absence of inhibitors using the synthetic substrate Mca-Lys-Ala-Met-His-Dpa-OH (SEQ ID NO:44 in the Sequence Listing provided herein). The synthetic substrate contains a modified amino acid (Dpa, (2,4-dinitrophenyl)-L-2,3-diaminopropionyl) and a fluorophore (Mca, (7-methoxycoumarin-4-yl)acetyl).

Activity is determined by measuring the fluorescence at λ_{ex} 328nm and λ_{em} 393nm. Percent inhibition is calculated as follows: % Inhibition is equal to the $[\text{Fluorescence}_{plus\ inhibitor} - \text{Fluorescence}_{background}]$ divided by the $[\text{Fluorescence}_{minus\ inhibitor} - \text{Fluorescence}_{background}]$.

A similar protocol is used for other expressed and purified CLCA hydrolase domains using substrates and buffers conditions optimal for the particular CLCA, for instance as described for MMPs in C. Graham Knight *et al.*, (1992) FEBS Lett. 296(3):263-266.

TABLE 1

	SEQRES	1	ASP	PRO	ASN	VAL	PRO	GLU	ASP	GLU	THR	LEU	ILE	GLN	GLN
	SEQRES	2	ILE	LYS	ASP	MET	VAL	THR	GLN	ALA	SER	LEU	TYR	LEU	PHE
	SEQRES	3	GLU	ALA	THR	GLY	LYS	ARG	PHE	TYR	PHE	LYS	ASN	VAL	ALA
5	SEQRES	4	ILE	LEU	ILE	PRO	GLU	THR	TRP	LYS	THR	LYS	ALA	ASP	TYR
	SEQRES	5	VAL	ARG	PRO	LYS	LEU	GLU	THR	TYR	LYS	ASN	ALA	ASP	VAL
	SEQRES	6	LEU	VAL	ALA	GLU	SER	THR	PRO	PRO	GLY	ASN	ASP	GLU	PRO
	SEQRES	7	TYR	THR	GLU	GLN	MET	GLY	ASN	CYS	GLY	GLU	LYS	GLY	GLU
	SEQRES	8	ARG	ILE	HIS	LEU	THR	PRO	ASP	PHE	ILE	ALA	GLY	LYS	LYS
10	SEQRES	9	LEU	ALA	GLU	TYR	GLY	PRO	GLN	GLY	LYS	ALA	PHE	VAL	HIS
	SEQRES	10	GLU	TRP	ALA	HIS	LEU	ARG	TRP	GLY	VAL	PHE	ASP	GLU	TYR
	SEQRES	11	ASN	ASN	ASP	GLU	LYS	PHE	TYR	LEU	SER	ASN	GLY	ARG	ILE
	SEQRES	12	GLN	ALA	VAL	ARG	CYS	SER	ALA	GLY	ILE	THR	GLY	THR	ASN
	SEQRES	13	VAL	VAL	LYS	LYS	CYS	GLN							
15	ATOM	1	N	ASP	40	4.369	-19.407	16.905	1.00	-0.99					
	ATOM	2	CA	ASP	40	4.984	-18.183	17.527	1.00	0.33					
	ATOM	3	C	ASP	40	3.866	-17.128	17.724	1.00	0.57					
	ATOM	4	O	ASP	40	3.494	-16.828	18.869	1.00	-0.57					
	ATOM	5	CB	ASP	40	6.271	-17.685	16.869	1.00	-0.11					
20	ATOM	6	CG	ASP	40	7.362	-18.755	16.736	1.00	0.91					
	ATOM	7	OD1	ASP	40	6.971	-19.962	16.831	1.00	-0.90					
	ATOM	8	OD2	ASP	40	8.533	-18.346	16.505	1.00	-0.90					
	ATOM	9	N	PRO	41	3.108	-16.686	16.657	1.00	-0.66					
	ATOM	10	CA	PRO	41	2.050	-15.682	16.840	1.00	0.36					
25	ATOM	11	C	PRO	41	0.714	-16.285	17.369	1.00	0.57					
	ATOM	12	O	PRO	41	-0.360	-15.688	17.332	1.00	-0.57					
	ATOM	13	CB	PRO	41	1.859	-15.087	15.446	1.00	0.00					
	ATOM	14	CG	PRO	41	2.199	-16.245	14.515	1.00	0.00					
	ATOM	15	CD	PRO	41	3.287	-17.017	15.255	1.00	0.30					
30	ATOM	16	N	ASN	42	0.837	-17.531	17.949	1.00	-0.73					
	ATOM	17	CA	ASN	42	-0.230	-18.189	18.691	1.00	0.36					
	ATOM	18	C	ASN	42	-0.121	-17.919	20.213	1.00	0.57					
	ATOM	19	O	ASN	42	-0.985	-18.305	21.003	1.00	-0.57					
	ATOM	20	CB	ASN	42	-0.144	-19.703	18.507	1.00	0.06					
35	ATOM	21	CG	ASN	42	-0.362	-20.112	17.072	1.00	0.57					
	ATOM	22	OD1	ASN	42	-1.415	-19.951	16.465	1.00	-0.57					
	ATOM	23	ND2	ASN	42	0.695	-20.754	16.486	1.00	-0.80					
	ATOM	24	N	VAL	43	1.070	-17.371	20.637	1.00	-0.73					
	ATOM	25	CA	VAL	43	1.358	-17.124	22.051	1.00	0.36					
40	ATOM	26	C	VAL	43	0.696	-15.775	22.438	1.00	0.57					
	ATOM	27	O	VAL	43	0.810	-14.772	21.728	1.00	-0.57					
	ATOM	28	CB	VAL	43	2.888	-17.069	22.293	1.00	0.00					
	ATOM	29	CG1	VAL	43	3.242	-16.895	23.773	1.00	0.00					
	ATOM	30	CG2	VAL	43	3.586	-18.340	21.790	1.00	0.00					
45	ATOM	31	N	PRO	44	0.031	-15.695	23.647	1.00	-0.66					
	ATOM	32	CA	PRO	44	-0.680	-14.469	24.048	1.00	0.36					
	ATOM	33	C	PRO	44	0.202	-13.408	24.759	1.00	0.57					
	ATOM	34	O	PRO	44	-0.291	-12.537	25.475	1.00	-0.57					
	ATOM	35	CB	PRO	44	-1.770	-14.981	24.999	1.00	0.00					
50	ATOM	36	CG	PRO	44	-1.131	-16.210	25.637	1.00	0.00					
	ATOM	37	CD	PRO	44	-0.321	-16.814	24.502	1.00	0.30					

	ATOM	38	N	GLU	45	1.542	-13.487	24.479	1.00	-0.73
	ATOM	39	CA	GLU	45	2.554	-12.572	25.027	1.00	0.36
	ATOM	40	C	GLU	45	2.867	-11.393	24.065	1.00	0.57
	ATOM	41	O	GLU	45	3.481	-10.405	24.466	1.00	-0.57
5	ATOM	42	CB	GLU	45	3.796	-13.401	25.397	1.00	0.00
	ATOM	43	CG	GLU	45	4.893	-12.627	26.131	1.00	-0.11
	ATOM	44	CD	GLU	45	5.904	-13.480	26.910	1.00	0.91
	ATOM	45	OE1	GLU	45	5.709	-14.728	26.925	1.00	-0.90
	ATOM	46	OE2	GLU	45	6.811	-12.821	27.500	1.00	-0.90
10	ATOM	47	N	ASP	46	2.437	-11.550	22.758	1.00	-0.73
	ATOM	48	CA	ASP	46	2.879	-10.670	21.649	1.00	0.36
	ATOM	49	C	ASP	46	4.311	-11.126	21.235	1.00	0.57
	ATOM	50	O	ASP	46	4.827	-12.151	21.690	1.00	-0.57
	ATOM	51	CB	ASP	46	2.726	-9.185	21.971	1.00	-0.11
15	ATOM	52	CG	ASP	46	2.615	-8.268	20.761	1.00	0.91
	ATOM	53	OD1	ASP	46	2.845	-8.794	19.636	1.00	-0.90
	ATOM	54	OD2	ASP	46	2.293	-7.071	21.018	1.00	-0.90
	ATOM	55	N	GLU	47	4.936	-10.362	20.282	1.00	-0.73
	ATOM	56	CA	GLU	47	6.253	-10.677	19.736	1.00	0.36
20	ATOM	57	C	GLU	47	6.940	-9.327	19.392	1.00	0.57
	ATOM	58	O	GLU	47	6.351	-8.330	18.971	1.00	-0.57
	ATOM	59	CB	GLU	47	6.124	-11.632	18.540	1.00	0.00
	ATOM	60	CG	GLU	47	7.447	-12.045	17.893	1.00	-0.11
	ATOM	61	CD	GLU	47	7.177	-12.833	16.604	1.00	0.91
25	ATOM	62	OE1	GLU	47	6.454	-13.859	16.720	1.00	-0.90
	ATOM	63	OE2	GLU	47	7.717	-12.345	15.568	1.00	-0.90
	ATOM	64	N	THR	48	8.312	-9.299	19.574	1.00	-0.73
	ATOM	65	CA	THR	48	9.076	-8.068	19.335	1.00	0.36
	ATOM	66	C	THR	48	9.395	-7.933	17.832	1.00	0.57
30	ATOM	67	O	THR	48	10.451	-8.322	17.332	1.00	-0.57
	ATOM	68	CB	THR	48	10.370	-8.030	20.183	1.00	0.28
	ATOM	69	OG1	THR	48	10.026	-7.847	21.567	1.00	-0.68
	ATOM	70	CG2	THR	48	11.296	-6.866	19.832	1.00	0.00
	ATOM	71	N	LEU	49	8.393	-7.340	17.090	1.00	-0.73
35	ATOM	72	CA	LEU	49	8.541	-7.129	15.654	1.00	0.36
	ATOM	73	C	LEU	49	9.316	-5.800	15.378	1.00	0.57
	ATOM	74	O	LEU	49	9.561	-4.938	16.224	1.00	-0.57
	ATOM	75	CB	LEU	49	7.198	-7.145	14.904	1.00	0.00
	ATOM	76	CG	LEU	49	6.592	-8.539	14.626	1.00	0.00
40	ATOM	77	CD1	LEU	49	7.556	-9.480	13.901	1.00	0.00
	ATOM	78	CD2	LEU	49	6.064	-9.203	15.888	1.00	0.00
	ATOM	79	N	ILE	50	9.768	-5.672	14.076	1.00	-0.73
	ATOM	80	CA	ILE	50	10.645	-4.595	13.644	1.00	0.36
	ATOM	81	C	ILE	50	9.788	-3.571	12.859	1.00	0.57
45	ATOM	82	O	ILE	50	8.989	-3.916	11.992	1.00	-0.57
	ATOM	83	CB	ILE	50	11.769	-5.134	12.710	1.00	0.00
	ATOM	84	CG1	ILE	50	12.672	-6.217	13.341	1.00	0.00
	ATOM	85	CG2	ILE	50	12.684	-3.995	12.237	1.00	0.00
	ATOM	86	CD1	ILE	50	12.006	-7.563	13.584	1.00	0.00
50	ATOM	87	N	GLN	51	10.070	-2.232	13.120	1.00	-0.73
	ATOM	88	CA	GLN	51	9.280	-1.203	12.420	1.00	0.36
	ATOM	89	C	GLN	51	9.828	-0.957	10.987	1.00	0.57

	ATOM	90	O	GLN	51	9.124	-0.551	10.064	1.00	-0.57
	ATOM	91	CB	GLN	51	9.182	0.109	13.222	1.00	0.00
	ATOM	92	CG	GLN	51	10.509	0.828	13.457	1.00	0.06
	ATOM	93	CD	GLN	51	10.479	2.075	14.321	1.00	0.57
5	ATOM	94	OE1	GLN	51	11.513	2.687	14.580	1.00	-0.57
	ATOM	95	NE2	GLN	51	9.293	2.493	14.828	1.00	-0.80
	ATOM	96	N	GLN	52	11.198	-1.052	10.844	1.00	-0.73
	ATOM	97	CA	GLN	52	11.877	-0.689	9.607	1.00	0.36
	ATOM	98	C	GLN	52	11.779	-1.788	8.521	1.00	0.57
10	ATOM	99	O	GLN	52	12.767	-2.429	8.151	1.00	-0.57
	ATOM	100	CB	GLN	52	13.376	-0.419	9.819	1.00	0.00
	ATOM	101	CG	GLN	52	13.673	0.864	10.569	1.00	0.06
	ATOM	102	CD	GLN	52	14.016	0.774	12.035	1.00	0.57
	ATOM	103	OE1	GLN	52	14.624	1.695	12.574	1.00	-0.57
15	ATOM	104	NE2	GLN	52	13.658	-0.334	12.732	1.00	-0.80
	ATOM	105	N	ILE	53	10.546	-1.932	7.943	1.00	-0.73
	ATOM	106	CA	ILE	53	10.362	-2.770	6.757	1.00	0.36
	ATOM	107	C	ILE	53	10.907	-1.982	5.523	1.00	0.57
	ATOM	108	O	ILE	53	10.936	-0.748	5.480	1.00	-0.57
20	ATOM	109	CB	ILE	53	8.894	-3.234	6.641	1.00	0.00
	ATOM	110	CG1	ILE	53	8.692	-4.461	5.736	1.00	0.00
	ATOM	111	CG2	ILE	53	7.951	-2.112	6.185	1.00	0.00
	ATOM	112	CD1	ILE	53	9.474	-5.693	6.165	1.00	0.00
	ATOM	113	N	LYS	54	11.409	-2.750	4.482	1.00	-0.73
25	ATOM	114	CA	LYS	54	11.666	-2.144	3.172	1.00	0.36
	ATOM	115	C	LYS	54	10.412	-2.358	2.293	1.00	0.57
	ATOM	116	O	LYS	54	9.660	-3.280	2.484	1.00	-0.57
	ATOM	117	CB	LYS	54	12.924	-2.713	2.480	1.00	0.00
	ATOM	118	CG	LYS	54	12.872	-4.215	2.164	1.00	0.00
30	ATOM	119	CD	LYS	54	14.009	-4.674	1.228	1.00	0.00
	ATOM	120	CE	LYS	54	13.901	-6.178	1.000	1.00	0.50
	ATOM	121	NZ	LYS	54	14.859	-6.667	0.002	1.00	-0.85
	ATOM	122	N	ASP	55	10.274	-1.460	1.243	1.00	-0.73
	ATOM	123	CA	ASP	55	9.338	-1.783	0.163	1.00	0.36
35	ATOM	124	C	ASP	55	10.145	-2.474	-0.961	1.00	0.57
	ATOM	125	O	ASP	55	11.375	-2.416	-1.024	1.00	-0.57
	ATOM	126	CB	ASP	55	8.564	-0.560	-0.314	1.00	-0.11
	ATOM	127	CG	ASP	55	9.271	0.163	-1.431	1.00	0.91
	ATOM	128	OD1	ASP	55	8.923	-0.100	-2.614	1.00	-0.90
40	ATOM	129	OD2	ASP	55	10.147	1.011	-1.090	1.00	-0.90
	ATOM	130	N	MET	56	9.366	-3.104	-1.906	1.00	-0.73
	ATOM	131	CA	MET	56	9.882	-3.302	-3.251	1.00	0.36
	ATOM	132	C	MET	56	8.663	-3.400	-4.193	1.00	0.57
	ATOM	133	O	MET	56	7.659	-4.057	-3.920	1.00	-0.57
45	ATOM	134	CB	MET	56	10.738	-4.566	-3.393	1.00	0.00
	ATOM	135	CG	MET	56	11.715	-4.427	-4.563	1.00	0.23
	ATOM	136	SD	MET	56	12.417	-6.029	-5.053	1.00	-0.46
	ATOM	137	CE	MET	56	11.094	-6.599	-6.148	1.00	0.23
	ATOM	138	N	VAL	57	8.812	-2.684	-5.353	1.00	-0.73
50	ATOM	139	CA	VAL	57	7.838	-2.708	-6.444	1.00	0.36
	ATOM	140	C	VAL	57	8.487	-3.633	-7.492	1.00	0.57
	ATOM	141	O	VAL	57	9.660	-3.469	-7.836	1.00	-0.57

	ATOM	142	CB VAL	57	7.651	-1.265	-6.965	1.00	0.00
	ATOM	143	CG1 VAL	57	6.739	-1.216	-8.182	1.00	0.00
	ATOM	144	CG2 VAL	57	7.080	-0.342	-5.881	1.00	0.00
	ATOM	145	N THR	58	7.713	-4.667	-7.968	1.00	-0.73
5	ATOM	146	CA THR	58	8.225	-5.554	-9.023	1.00	0.36
	ATOM	147	C THR	58	8.028	-4.921	-10.415	1.00	0.57
	ATOM	148	O THR	58	8.764	-5.183	-11.364	1.00	-0.57
	ATOM	149	CB THR	58	7.563	-6.945	-9.029	1.00	0.28
	ATOM	150	OG1 THR	58	6.135	-6.841	-9.071	1.00	-0.68
10	ATOM	151	CG2 THR	58	7.939	-7.767	-7.801	1.00	0.00
	ATOM	152	N GLN	59	6.893	-4.162	-10.544	1.00	-0.73
	ATOM	153	CA GLN	59	6.518	-3.457	-11.763	1.00	0.36
	ATOM	154	C GLN	59	5.703	-2.243	-11.287	1.00	0.57
	ATOM	155	O GLN	59	4.911	-2.330	-10.349	1.00	-0.57
15	ATOM	156	CB GLN	59	5.681	-4.345	-12.687	1.00	0.00
	ATOM	157	CG GLN	59	5.366	-3.662	-14.015	1.00	0.06
	ATOM	158	CD GLN	59	4.595	-4.587	-14.925	1.00	0.57
	ATOM	159	OE1 GLN	59	5.104	-5.557	-15.479	1.00	-0.57
	ATOM	160	NE2 GLN	59	3.283	-4.274	-15.088	1.00	-0.80
20	ATOM	161	N ALA	60	5.973	-1.070	-11.955	1.00	-0.73
	ATOM	162	CA ALA	60	5.017	0.035	-11.935	1.00	0.36
	ATOM	163	C ALA	60	4.446	0.092	-13.360	1.00	0.57
	ATOM	164	O ALA	60	5.135	-0.225	-14.335	1.00	-0.57
	ATOM	165	CB ALA	60	5.714	1.352	-11.627	1.00	0.00
25	ATOM	166	N SER	61	3.154	0.567	-13.464	1.00	-0.73
	ATOM	167	CA SER	61	2.527	0.441	-14.776	1.00	0.36
	ATOM	168	C SER	61	3.247	1.374	-15.775	1.00	0.57
	ATOM	169	O SER	61	3.753	2.457	-15.467	1.00	-0.57
	ATOM	170	CB SER	61	1.038	0.808	-14.743	1.00	0.28
30	ATOM	171	OG SER	61	0.850	2.168	-14.331	1.00	-0.68
	ATOM	172	N LEU	62	3.183	0.962	-17.098	1.00	-0.73
	ATOM	173	CA LEU	62	4.075	1.563	-18.098	1.00	0.36
	ATOM	174	C LEU	62	3.845	3.063	-18.425	1.00	0.57
	ATOM	175	O LEU	62	4.534	3.672	-19.243	1.00	-0.57
35	ATOM	176	CB LEU	62	4.040	0.763	-19.419	1.00	0.00
	ATOM	177	CG LEU	62	2.796	0.973	-20.317	1.00	0.00
	ATOM	178	CD1 LEU	62	2.990	0.237	-21.645	1.00	0.00
	ATOM	179	CD2 LEU	62	1.492	0.515	-19.666	1.00	0.00
	ATOM	180	N TYR	63	2.782	3.642	-17.781	1.00	-0.73
40	ATOM	181	CA TYR	63	2.408	5.033	-17.959	1.00	0.36
	ATOM	182	C TYR	63	3.295	5.989	-17.124	1.00	0.57
	ATOM	183	O TYR	63	3.304	7.205	-17.344	1.00	-0.57
	ATOM	184	CB TYR	63	0.933	5.252	-17.582	1.00	0.14
	ATOM	185	CG TYR	63	-0.033	4.385	-18.366	1.00	-0.14
45	ATOM	186	CD1 TYR	63	-0.288	4.638	-19.722	1.00	-0.15
	ATOM	187	CD2 TYR	63	-0.673	3.300	-17.748	1.00	-0.15
	ATOM	188	CE1 TYR	63	-1.172	3.828	-20.441	1.00	-0.15
	ATOM	189	CE2 TYR	63	-1.560	2.494	-18.464	1.00	-0.15
	ATOM	190	CZ TYR	63	-1.806	2.767	-19.803	1.00	0.08
50	ATOM	191	OH TYR	63	-2.686	1.967	-20.468	1.00	-0.53
	ATOM	192	N LEU	64	3.965	5.426	-16.056	1.00	-0.73
	ATOM	193	CA LEU	64	4.896	6.189	-15.244	1.00	0.36

	ATOM	194	C	LEU	64	6.359	5.745	-15.508	1.00	0.57
	ATOM	195	O	LEU	64	6.685	4.588	-15.754	1.00	-0.57
	ATOM	196	CB	LEU	64	4.615	6.051	-13.734	1.00	0.00
	ATOM	197	CG	LEU	64	3.283	6.676	-13.266	1.00	0.00
5	ATOM	198	CD1	LEU	64	2.088	5.754	-13.503	1.00	0.00
	ATOM	199	CD2	LEU	64	3.354	7.002	-11.771	1.00	0.00
	ATOM	200	N	PHE	65	7.293	6.757	-15.335	1.00	-0.73
	ATOM	201	CA	PHE	65	8.706	6.427	-15.074	1.00	0.36
	ATOM	202	C	PHE	65	8.769	6.241	-13.544	1.00	0.57
10	ATOM	203	O	PHE	65	8.110	6.964	-12.785	1.00	-0.57
	ATOM	204	CB	PHE	65	9.612	7.587	-15.508	1.00	0.14
	ATOM	205	CG	PHE	65	11.082	7.314	-15.314	1.00	-0.14
	ATOM	206	CD1	PHE	65	11.803	6.579	-16.263	1.00	-0.15
	ATOM	207	CD2	PHE	65	11.739	7.764	-14.160	1.00	-0.15
15	ATOM	208	CE1	PHE	65	13.154	6.294	-16.056	1.00	-0.15
	ATOM	209	CE2	PHE	65	13.086	7.466	-13.950	1.00	-0.15
	ATOM	210	CZ	PHE	65	13.793	6.732	-14.898	1.00	-0.15
	ATOM	211	N	GLU	66	9.609	5.252	-13.070	1.00	-0.73
	ATOM	212	CA	GLU	66	9.395	4.762	-11.708	1.00	0.36
20	ATOM	213	C	GLU	66	9.608	5.874	-10.654	1.00	0.57
	ATOM	214	O	GLU	66	8.893	5.947	-9.651	1.00	-0.57
	ATOM	215	CB	GLU	66	10.122	3.444	-11.406	1.00	0.00
	ATOM	216	CG	GLU	66	11.644	3.504	-11.348	1.00	-0.11
	ATOM	217	CD	GLU	66	12.112	4.260	-10.110	1.00	0.91
25	ATOM	218	OE1	GLU	66	11.677	3.841	-9.004	1.00	-0.90
	ATOM	219	OE2	GLU	66	12.780	5.301	-10.372	1.00	-0.90
	ATOM	220	N	ALA	67	10.592	6.811	-10.923	1.00	-0.73
	ATOM	221	CA	ALA	67	10.971	7.758	-9.873	1.00	0.36
	ATOM	222	C	ALA	67	9.802	8.707	-9.551	1.00	0.57
30	ATOM	223	O	ALA	67	9.616	9.168	-8.423	1.00	-0.57
	ATOM	224	CB	ALA	67	12.163	8.606	-10.297	1.00	0.00
	ATOM	225	N	THR	68	9.016	9.078	-10.637	1.00	-0.73
	ATOM	226	CA	THR	68	7.828	9.886	-10.398	1.00	0.36
	ATOM	227	C	THR	68	6.655	9.077	-9.812	1.00	0.57
35	ATOM	228	O	THR	68	5.652	9.653	-9.390	1.00	-0.57
	ATOM	229	CB	THR	68	7.347	10.722	-11.605	1.00	0.28
	ATOM	230	OG1	THR	68	6.380	11.705	-11.187	1.00	-0.68
	ATOM	231	CG2	THR	68	6.745	9.921	-12.750	1.00	0.00
	ATOM	232	N	GLY	69	6.766	7.712	-9.837	1.00	-0.73
40	ATOM	233	CA	GLY	69	5.872	6.857	-9.084	1.00	0.36
	ATOM	234	C	GLY	69	6.308	6.799	-7.615	1.00	0.57
	ATOM	235	O	GLY	69	5.495	6.871	-6.691	1.00	-0.57
	ATOM	236	N	LYS	70	7.660	6.644	-7.394	1.00	-0.73
	ATOM	237	CA	LYS	70	8.221	6.548	-6.047	1.00	0.36
45	ATOM	238	C	LYS	70	7.995	7.879	-5.290	1.00	0.57
	ATOM	239	O	LYS	70	7.894	7.929	-4.063	1.00	-0.57
	ATOM	240	CB	LYS	70	9.716	6.217	-6.052	1.00	0.00
	ATOM	241	CG	LYS	70	10.019	4.734	-6.296	1.00	0.00
	ATOM	242	CD	LYS	70	9.740	3.843	-5.080	1.00	0.00
50	ATOM	243	CE	LYS	70	10.084	2.389	-5.381	1.00	0.50
	ATOM	244	NZ	LYS	70	9.915	1.592	-4.167	1.00	-0.85
	ATOM	245	N	ARG	71	7.936	8.997	-6.104	1.00	-0.73

	ATOM	246	CA	ARG	71	7.758	10.342	-5.559	1.00	0.36
	ATOM	247	C	ARG	71	6.378	10.440	-4.873	1.00	0.57
	ATOM	248	O	ARG	71	6.172	11.198	-3.926	1.00	-0.57
	ATOM	249	CB	ARG	71	7.808	11.368	-6.704	1.00	0.00
5	ATOM	250	CG	ARG	71	7.520	12.804	-6.269	1.00	0.00
	ATOM	251	CD	ARG	71	7.417	13.744	-7.464	1.00	0.33
	ATOM	252	NE	ARG	71	6.928	15.071	-7.057	1.00	-0.84
	ATOM	253	CZ	ARG	71	5.660	15.358	-6.716	1.00	1.20
	ATOM	254	NH1	ARG	71	4.685	14.450	-6.755	1.00	-0.97
10	ATOM	255	NH2	ARG	71	5.355	16.601	-6.326	1.00	-0.97
	ATOM	256	N	PHE	72	5.351	9.777	-5.516	1.00	-0.73
	ATOM	257	CA	PHE	72	4.043	9.687	-4.873	1.00	0.36
	ATOM	258	C	PHE	72	4.022	8.552	-3.834	1.00	0.57
	ATOM	259	O	PHE	72	3.291	8.613	-2.845	1.00	-0.57
15	ATOM	260	CB	PHE	72	2.908	9.469	-5.878	1.00	0.14
	ATOM	261	CG	PHE	72	2.618	10.701	-6.709	1.00	-0.14
	ATOM	262	CD1	PHE	72	2.978	10.749	-8.058	1.00	-0.15
	ATOM	263	CD2	PHE	72	1.960	11.803	-6.149	1.00	-0.15
	ATOM	264	CE1	PHE	72	2.695	11.875	-8.833	1.00	-0.15
20	ATOM	265	CE2	PHE	72	1.648	12.918	-6.930	1.00	-0.15
	ATOM	266	CZ	PHE	72	2.022	12.957	-8.272	1.00	-0.15
	ATOM	267	N	TYR	73	4.793	7.438	-4.116	1.00	-0.73
	ATOM	268	CA	TYR	73	4.615	6.214	-3.329	1.00	0.36
	ATOM	269	C	TYR	73	4.925	6.514	-1.854	1.00	0.57
25	ATOM	270	O	TYR	73	4.280	6.029	-0.924	1.00	-0.57
	ATOM	271	CB	TYR	73	5.542	5.086	-3.816	1.00	0.14
	ATOM	272	CG	TYR	73	5.276	3.747	-3.169	1.00	-0.14
	ATOM	273	CD1	TYR	73	5.790	3.463	-1.893	1.00	-0.15
	ATOM	274	CD2	TYR	73	4.467	2.797	-3.805	1.00	-0.15
30	ATOM	275	CE1	TYR	73	5.443	2.289	-1.231	1.00	-0.15
	ATOM	276	CE2	TYR	73	4.144	1.607	-3.154	1.00	-0.15
	ATOM	277	CZ	TYR	73	4.615	1.378	-1.868	1.00	0.08
	ATOM	278	OH	TYR	73	4.236	0.237	-1.233	1.00	-0.53
	ATOM	279	N	PHE	74	6.037	7.301	-1.597	1.00	-0.73
35	ATOM	280	CA	PHE	74	6.487	7.388	-0.207	1.00	0.36
	ATOM	281	C	PHE	74	5.415	8.093	0.665	1.00	0.57
	ATOM	282	O	PHE	74	5.366	7.954	1.886	1.00	-0.57
	ATOM	283	CB	PHE	74	7.881	8.008	-0.032	1.00	0.14
	ATOM	284	CG	PHE	74	7.955	9.516	0.016	1.00	-0.14
40	ATOM	285	CD1	PHE	74	8.322	10.171	1.203	1.00	-0.15
	ATOM	286	CD2	PHE	74	7.675	10.285	-1.116	1.00	-0.15
	ATOM	287	CE1	PHE	74	8.404	11.564	1.252	1.00	-0.15
	ATOM	288	CE2	PHE	74	7.742	11.678	-1.062	1.00	-0.15
	ATOM	289	CZ	PHE	74	8.108	12.319	0.120	1.00	-0.15
45	ATOM	290	N	LYS	75	4.579	8.951	-0.019	1.00	-0.73
	ATOM	291	CA	LYS	75	3.446	9.633	0.585	1.00	0.36
	ATOM	292	C	LYS	75	2.083	9.047	0.153	1.00	0.57
	ATOM	293	O	LYS	75	1.054	9.725	0.143	1.00	-0.57
	ATOM	294	CB	LYS	75	3.527	11.146	0.307	1.00	0.00
50	ATOM	295	CG	LYS	75	4.546	11.853	1.210	1.00	0.00
	ATOM	296	CD	LYS	75	4.016	12.072	2.630	1.00	0.00
	ATOM	297	CE	LYS	75	5.118	12.545	3.568	1.00	0.50

	ATOM	298	NZ	LYS	75	4.568	12.679	4.933	1.00	-0.85
	ATOM	299	N	ASN	76	2.050	7.681	-0.037	1.00	-0.73
	ATOM	300	CA	ASN	76	0.815	6.935	0.214	1.00	0.36
	ATOM	301	C	ASN	76	0.854	6.435	1.675	1.00	0.57
5	ATOM	302	O	ASN	76	-0.089	6.608	2.444	1.00	-0.57
	ATOM	303	CB	ASN	76	0.500	5.881	-0.841	1.00	0.06
	ATOM	304	CG	ASN	76	1.537	4.805	-0.996	1.00	0.57
	ATOM	305	OD1	ASN	76	2.127	4.286	-0.045	1.00	-0.57
	ATOM	306	ND2	ASN	76	1.796	4.396	-2.261	1.00	-0.80
10	ATOM	307	N	VAL	77	2.019	5.789	2.059	1.00	-0.73
	ATOM	308	CA	VAL	77	2.080	5.190	3.390	1.00	0.36
	ATOM	309	C	VAL	77	2.289	6.298	4.451	1.00	0.57
	ATOM	310	O	VAL	77	1.748	6.276	5.559	1.00	-0.57
	ATOM	311	CB	VAL	77	3.177	4.108	3.518	1.00	0.00
15	ATOM	312	CG1	VAL	77	2.751	2.788	2.873	1.00	0.00
	ATOM	313	CG2	VAL	77	4.554	4.519	2.989	1.00	0.00
	ATOM	314	N	ALA	78	3.203	7.286	4.132	1.00	-0.73
	ATOM	315	CA	ALA	78	3.752	8.169	5.155	1.00	0.36
	ATOM	316	C	ALA	78	2.846	9.385	5.470	1.00	0.57
20	ATOM	317	O	ALA	78	3.291	10.533	5.579	1.00	-0.57
	ATOM	318	CB	ALA	78	5.158	8.635	4.792	1.00	0.00
	ATOM	319	N	ILE	79	1.539	9.066	5.735	1.00	-0.73
	ATOM	320	CA	ILE	79	0.480	10.036	6.010	1.00	0.36
	ATOM	321	C	ILE	79	-0.725	9.292	6.643	1.00	0.57
25	ATOM	322	O	ILE	79	-1.894	9.497	6.326	1.00	-0.57
	ATOM	323	CB	ILE	79	0.143	10.898	4.761	1.00	0.00
	ATOM	324	CG1	ILE	79	-0.811	12.058	5.120	1.00	0.00
	ATOM	325	CG2	ILE	79	-0.367	10.061	3.582	1.00	0.00
	ATOM	326	CD1	ILE	79	-0.938	13.108	4.025	1.00	0.00
30	ATOM	327	N	LEU	80	-0.378	8.454	7.691	1.00	-0.73
	ATOM	328	CA	LEU	80	-1.387	7.590	8.304	1.00	0.36
	ATOM	329	C	LEU	80	-1.177	7.542	9.834	1.00	0.57
	ATOM	330	O	LEU	80	-1.956	8.099	10.609	1.00	-0.57
	ATOM	331	CB	LEU	80	-1.385	6.210	7.618	1.00	0.00
35	ATOM	332	CG	LEU	80	-2.765	5.526	7.568	1.00	0.00
	ATOM	333	CD1	LEU	80	-2.666	4.222	6.769	1.00	0.00
	ATOM	334	CD2	LEU	80	-3.342	5.238	8.951	1.00	0.00
	ATOM	335	N	ILE	81	-0.074	6.855	10.285	1.00	-0.73
	ATOM	336	CA	ILE	81	0.124	6.532	11.715	1.00	0.36
40	ATOM	337	C	ILE	81	1.622	6.135	11.854	1.00	0.57
	ATOM	338	O	ILE	81	2.238	5.734	10.856	1.00	-0.57
	ATOM	339	CB	ILE	81	-0.854	5.396	12.131	1.00	0.00
	ATOM	340	CG1	ILE	81	-1.044	5.206	13.647	1.00	0.00
	ATOM	341	CG2	ILE	81	-0.468	4.050	11.500	1.00	0.00
45	ATOM	342	CD1	ILE	81	-1.682	6.396	14.350	1.00	0.00
	ATOM	343	N	PRO	82	2.223	6.154	13.099	1.00	-0.66
	ATOM	344	CA	PRO	82	3.639	5.759	13.267	1.00	0.36
	ATOM	345	C	PRO	82	3.988	4.251	13.139	1.00	0.57
	ATOM	346	O	PRO	82	4.641	3.636	13.983	1.00	-0.57
50	ATOM	347	CB	PRO	82	4.003	6.272	14.665	1.00	0.00
	ATOM	348	CG	PRO	82	3.145	7.514	14.806	1.00	0.00
	ATOM	349	CD	PRO	82	1.838	7.084	14.159	1.00	0.30

	ATOM	350	N	GLU	83	3.644	3.677	11.930	1.00	-0.73
	ATOM	351	CA	GLU	83	4.482	2.596	11.391	1.00	0.36
	ATOM	352	C	GLU	83	5.715	3.293	10.738	1.00	0.57
	ATOM	353	O	GLU	83	5.890	4.513	10.820	1.00	-0.57
5	ATOM	354	CB	GLU	83	3.699	1.772	10.376	1.00	0.00
	ATOM	355	CG	GLU	83	2.492	1.036	10.950	1.00	-0.11
	ATOM	356	CD	GLU	83	1.629	0.466	9.830	1.00	0.91
	ATOM	357	OE1	GLU	83	2.065	0.533	8.654	1.00	-0.90
	ATOM	358	OE2	GLU	83	0.503	0.008	10.218	1.00	-0.90
10	ATOM	359	N	THR	84	6.649	2.483	10.120	1.00	-0.73
	ATOM	360	CA	THR	84	7.729	3.099	9.334	1.00	0.36
	ATOM	361	C	THR	84	7.977	2.225	8.090	1.00	0.57
	ATOM	362	O	THR	84	7.642	1.041	8.065	1.00	-0.57
	ATOM	363	CB	THR	84	9.048	3.280	10.120	1.00	0.28
15	ATOM	364	OG1	THR	84	9.724	2.047	10.390	1.00	-0.68
	ATOM	365	CG2	THR	84	8.874	3.987	11.458	1.00	0.00
	ATOM	366	N	TRP	85	8.635	2.840	7.040	1.00	-0.73
	ATOM	367	CA	TRP	85	8.593	2.220	5.708	1.00	0.36
	ATOM	368	C	TRP	85	9.879	2.686	5.002	1.00	0.57
20	ATOM	369	O	TRP	85	9.980	3.751	4.386	1.00	-0.57
	ATOM	370	CB	TRP	85	7.354	2.643	4.887	1.00	0.18
	ATOM	371	CG	TRP	85	6.080	2.714	5.675	1.00	-0.18
	ATOM	372	CD1	TRP	85	5.159	1.706	5.884	1.00	-0.30
	ATOM	373	CD2	TRP	85	5.617	3.856	6.406	1.00	0.00
25	ATOM	374	NE1	TRP	85	4.177	2.173	6.725	1.00	0.03
	ATOM	375	CE2	TRP	85	4.426	3.496	7.033	1.00	-0.15
	ATOM	376	CE3	TRP	85	6.125	5.157	6.613	1.00	-0.15
	ATOM	377	CZ2	TRP	85	3.696	4.392	7.821	1.00	-0.15
	ATOM	378	CZ3	TRP	85	5.455	6.027	7.476	1.00	-0.15
30	ATOM	379	CH2	TRP	85	4.249	5.651	8.059	1.00	-0.15
	ATOM	380	N	LYS	86	10.987	1.900	5.213	1.00	-0.73
	ATOM	381	CA	LYS	86	12.335	2.318	4.855	1.00	0.36
	ATOM	382	C	LYS	86	12.607	2.096	3.333	1.00	0.57
	ATOM	383	O	LYS	86	13.477	1.346	2.927	1.00	-0.57
35	ATOM	384	CB	LYS	86	13.367	1.571	5.735	1.00	0.00
	ATOM	385	CG	LYS	86	14.575	2.457	6.079	1.00	0.00
	ATOM	386	CD	LYS	86	15.681	1.684	6.812	1.00	0.00
	ATOM	387	CE	LYS	86	16.720	2.598	7.466	1.00	0.50
	ATOM	388	NZ	LYS	86	16.238	3.108	8.770	1.00	-0.85
40	ATOM	389	N	THR	87	11.881	2.930	2.496	1.00	-0.73
	ATOM	390	CA	THR	87	11.636	2.635	1.065	1.00	0.36
	ATOM	391	C	THR	87	12.915	2.326	0.240	1.00	0.57
	ATOM	392	O	THR	87	14.009	2.846	0.478	1.00	-0.57
	ATOM	393	CB	THR	87	10.860	3.804	0.391	1.00	0.28
45	ATOM	394	OG1	THR	87	10.485	3.535	-0.962	1.00	-0.68
	ATOM	395	CG2	THR	87	11.632	5.123	0.399	1.00	0.00
	ATOM	396	N	LYS	88	12.764	1.392	-0.759	1.00	-0.73
	ATOM	397	CA	LYS	88	13.855	0.883	-1.594	1.00	0.36
	ATOM	398	C	LYS	88	13.399	0.695	-3.058	1.00	0.57
50	ATOM	399	O	LYS	88	12.230	0.822	-3.411	1.00	-0.57
	ATOM	400	CB	LYS	88	14.345	-0.458	-1.011	1.00	0.00
	ATOM	401	CG	LYS	88	15.869	-0.608	-0.880	1.00	0.00

	ATOM	402	CD	LYS	88	16.582	0.454	-0.032	1.00	0.00
	ATOM	403	CE	LYS	88	16.100	0.504	1.411	1.00	0.50
	ATOM	404	NZ	LYS	88	15.856	1.895	1.813	1.00	-0.85
	ATOM	405	N	ALA	89	14.406	0.337	-3.931	1.00	-0.73
5	ATOM	406	CA	ALA	89	14.168	0.209	-5.376	1.00	0.36
	ATOM	407	C	ALA	89	15.119	-0.847	-5.973	1.00	0.57
	ATOM	408	O	ALA	89	15.558	-0.790	-7.116	1.00	-0.57
	ATOM	409	CB	ALA	89	14.346	1.557	-6.066	1.00	0.00
	ATOM	410	N	ASP	90	15.367	-1.929	-5.149	1.00	-0.73
10	ATOM	411	CA	ASP	90	16.340	-2.952	-5.535	1.00	0.36
	ATOM	412	C	ASP	90	16.135	-4.205	-4.653	1.00	0.57
	ATOM	413	O	ASP	90	15.834	-4.124	-3.452	1.00	-0.57
	ATOM	414	CB	ASP	90	17.753	-2.421	-5.338	1.00	-0.11
	ATOM	415	CG	ASP	90	18.838	-3.272	-5.933	1.00	0.91
15	ATOM	416	OD1	ASP	90	18.559	-4.385	-6.468	1.00	-0.90
	ATOM	417	OD2	ASP	90	20.024	-2.835	-5.817	1.00	-0.90
	ATOM	418	N	TYR	91	16.346	-5.389	-5.319	1.00	-0.73
	ATOM	419	CA	TYR	91	16.595	-6.671	-4.675	1.00	0.36
	ATOM	420	C	TYR	91	15.548	-7.154	-3.642	1.00	0.57
20	ATOM	421	O	TYR	91	15.416	-6.708	-2.501	1.00	-0.57
	ATOM	422	CB	TYR	91	18.002	-6.763	-4.058	1.00	0.14
	ATOM	423	CG	TYR	91	18.845	-7.870	-4.671	1.00	-0.14
	ATOM	424	CD1	TYR	91	19.204	-7.847	-6.027	1.00	-0.15
	ATOM	425	CD2	TYR	91	19.310	-8.924	-3.877	1.00	-0.15
25	ATOM	426	CE1	TYR	91	20.005	-8.857	-6.573	1.00	-0.15
	ATOM	427	CE2	TYR	91	20.117	-9.927	-4.414	1.00	-0.15
	ATOM	428	CZ	TYR	91	20.456	-9.890	-5.758	1.00	0.08
	ATOM	429	OH	TYR	91	21.241	-10.895	-6.237	1.00	-0.53
	ATOM	430	N	VAL	92	14.798	-8.235	-4.094	1.00	-0.73
30	ATOM	431	CA	VAL	92	13.786	-8.821	-3.206	1.00	0.36
	ATOM	432	C	VAL	92	14.527	-9.419	-1.983	1.00	0.57
	ATOM	433	O	VAL	92	14.196	-9.189	-0.820	1.00	-0.57
	ATOM	434	CB	VAL	92	12.912	-9.849	-3.966	1.00	0.00
	ATOM	435	CG1	VAL	92	13.689	-10.944	-4.703	1.00	0.00
35	ATOM	436	CG2	VAL	92	11.866	-10.486	-3.052	1.00	0.00
	ATOM	437	N	ARG	93	15.588	-10.233	-2.300	1.00	-0.73
	ATOM	438	CA	ARG	93	16.404	-10.870	-1.269	1.00	0.36
	ATOM	439	C	ARG	93	17.412	-9.847	-0.675	1.00	0.57
	ATOM	440	O	ARG	93	17.419	-8.658	-1.015	1.00	-0.57
40	ATOM	441	CB	ARG	93	17.079	-12.099	-1.908	1.00	0.00
	ATOM	442	CG	ARG	93	16.131	-13.306	-1.891	1.00	0.00
	ATOM	443	CD	ARG	93	16.696	-14.534	-2.595	1.00	0.33
	ATOM	444	NE	ARG	93	17.794	-15.153	-1.835	1.00	-0.84
	ATOM	445	CZ	ARG	93	19.108	-15.004	-2.057	1.00	1.20
45	ATOM	446	NH1	ARG	93	19.588	-14.193	-3.002	1.00	-0.97
	ATOM	447	NH2	ARG	93	19.977	-15.678	-1.296	1.00	-0.97
	ATOM	448	N	PRO	94	18.313	-10.296	0.264	1.00	-0.66
	ATOM	449	CA	PRO	94	19.409	-9.432	0.722	1.00	0.36
	ATOM	450	C	PRO	94	20.461	-9.291	-0.397	1.00	0.57
50	ATOM	451	O	PRO	94	20.852	-10.264	-1.042	1.00	-0.57
	ATOM	452	CB	PRO	94	20.014	-10.180	1.912	1.00	0.00
	ATOM	453	CG	PRO	94	18.882	-11.082	2.389	1.00	0.00

	ATOM	454	CD	PRO	94	18.193	-11.480	1.098	1.00	0.30
	ATOM	455	N	LYS	95	20.896	-8.002	-0.625	1.00	-0.73
	ATOM	456	CA	LYS	95	21.964	-7.687	-1.593	1.00	0.36
	ATOM	457	C	LYS	95	23.301	-7.411	-0.875	1.00	0.57
5	ATOM	458	O	LYS	95	24.351	-7.293	-1.497	1.00	-0.57
	ATOM	459	CB	LYS	95	21.578	-6.446	-2.420	1.00	0.00
	ATOM	460	CG	LYS	95	22.251	-6.426	-3.804	1.00	0.00
	ATOM	461	CD	LYS	95	21.687	-5.307	-4.681	1.00	0.00
	ATOM	462	CE	LYS	95	22.148	-5.404	-6.131	1.00	0.50
10	ATOM	463	NZ	LYS	95	21.304	-4.541	-6.964	1.00	-0.85
	ATOM	464	N	LEU	96	23.176	-7.164	0.474	1.00	-0.73
	ATOM	465	CA	LEU	96	24.326	-6.832	1.323	1.00	0.36
	ATOM	466	C	LEU	96	24.282	-7.821	2.514	1.00	0.57
	ATOM	467	O	LEU	96	23.303	-8.546	2.724	1.00	-0.57
15	ATOM	468	CB	LEU	96	24.215	-5.384	1.824	1.00	0.00
	ATOM	469	CG	LEU	96	24.185	-4.316	0.712	1.00	0.00
	ATOM	470	CD1	LEU	96	23.885	-2.943	1.319	1.00	0.00
	ATOM	471	CD2	LEU	96	25.498	-4.255	-0.069	1.00	0.00
	ATOM	472	N	GLU	97	25.385	-7.778	3.321	1.00	-0.73
20	ATOM	473	CA	GLU	97	25.617	-8.659	4.460	1.00	0.36
	ATOM	474	C	GLU	97	24.578	-8.460	5.586	1.00	0.57
	ATOM	475	O	GLU	97	24.173	-9.390	6.288	1.00	-0.57
	ATOM	476	CB	GLU	97	27.054	-8.501	5.009	1.00	0.00
	ATOM	477	CG	GLU	97	27.402	-7.153	5.664	1.00	-0.11
25	ATOM	478	CD	GLU	97	26.955	-5.973	4.809	1.00	0.91
	ATOM	479	OE1	GLU	97	27.353	-5.986	3.612	1.00	-0.90
	ATOM	480	OE2	GLU	97	26.066	-5.239	5.334	1.00	-0.90
	ATOM	481	N	THR	98	24.180	-7.171	5.828	1.00	-0.73
	ATOM	482	CA	THR	98	23.380	-6.765	6.977	1.00	0.36
30	ATOM	483	C	THR	98	21.888	-7.046	6.680	1.00	0.57
	ATOM	484	O	THR	98	20.989	-6.210	6.793	1.00	-0.57
	ATOM	485	CB	THR	98	23.596	-5.286	7.386	1.00	0.28
	ATOM	486	OG1	THR	98	23.758	-4.431	6.254	1.00	-0.68
	ATOM	487	CG2	THR	98	24.776	-5.114	8.338	1.00	0.00
35	ATOM	488	N	TYR	99	21.576	-8.373	6.478	1.00	-0.73
	ATOM	489	CA	TYR	99	20.382	-8.803	5.759	1.00	0.36
	ATOM	490	C	TYR	99	19.027	-8.331	6.357	1.00	0.57
	ATOM	491	O	TYR	99	18.820	-8.168	7.560	1.00	-0.57
	ATOM	492	CB	TYR	99	20.340	-10.344	5.625	1.00	0.14
40	ATOM	493	CG	TYR	99	20.412	-11.080	6.947	1.00	-0.14
	ATOM	494	CD1	TYR	99	21.644	-11.545	7.432	1.00	-0.15
	ATOM	495	CD2	TYR	99	19.266	-11.251	7.737	1.00	-0.15
	ATOM	496	CE1	TYR	99	21.736	-12.129	8.697	1.00	-0.15
	ATOM	497	CE2	TYR	99	19.360	-11.823	9.005	1.00	-0.15
45	ATOM	498	CZ	TYR	99	20.594	-12.250	9.479	1.00	0.08
	ATOM	499	OH	TYR	99	20.638	-12.778	10.733	1.00	-0.53
	ATOM	500	N	LYS	100	18.021	-8.145	5.425	1.00	-0.73
	ATOM	501	CA	LYS	100	16.600	-8.070	5.792	1.00	0.36
	ATOM	502	C	LYS	100	15.821	-8.710	4.614	1.00	0.57
50	ATOM	503	O	LYS	100	16.280	-8.708	3.468	1.00	-0.57
	ATOM	504	CB	LYS	100	16.096	-6.635	6.032	1.00	0.00
	ATOM	505	CG	LYS	100	16.607	-5.989	7.329	1.00	0.00

	ATOM	506	CD	LYS	100	17.871	-5.142	7.134	1.00	0.00
	ATOM	507	CE	LYS	100	18.626	-4.893	8.440	1.00	0.50
	ATOM	508	NZ	LYS	100	19.383	-6.085	8.834	1.00	-0.85
	ATOM	509	N	ASN	101	14.615	-9.271	4.953	1.00	-0.73
5	ATOM	510	CA	ASN	101	13.745	-9.928	3.963	1.00	0.36
	ATOM	511	C	ASN	101	12.840	-8.865	3.279	1.00	0.57
	ATOM	512	O	ASN	101	12.745	-7.706	3.682	1.00	-0.57
	ATOM	513	CB	ASN	101	12.932	-11.019	4.661	1.00	0.06
	ATOM	514	CG	ASN	101	12.176	-11.883	3.685	1.00	0.57
10	ATOM	515	OD1	ASN	101	12.490	-11.983	2.499	1.00	-0.57
	ATOM	516	ND2	ASN	101	11.140	-12.587	4.208	1.00	-0.80
	ATOM	517	N	ALA	102	12.212	-9.287	2.124	1.00	-0.73
	ATOM	518	CA	ALA	102	11.059	-8.589	1.555	1.00	0.36
	ATOM	519	C	ALA	102	9.797	-9.337	2.007	1.00	0.57
15	ATOM	520	O	ALA	102	9.292	-10.260	1.365	1.00	-0.57
	ATOM	521	CB	ALA	102	11.112	-8.619	0.036	1.00	0.00
	ATOM	522	N	ASP	103	9.320	-8.940	3.235	1.00	-0.73
	ATOM	523	CA	ASP	103	8.204	-9.683	3.836	1.00	0.36
	ATOM	524	C	ASP	103	6.918	-9.203	3.123	1.00	0.57
20	ATOM	525	O	ASP	103	5.948	-9.946	2.944	1.00	-0.57
	ATOM	526	CB	ASP	103	8.113	-9.478	5.338	1.00	-0.11
	ATOM	527	CG	ASP	103	9.441	-10.045	5.789	1.00	0.91
	ATOM	528	OD1	ASP	103	10.384	-9.205	5.864	1.00	-0.90
	ATOM	529	OD2	ASP	103	9.513	-11.305	5.873	1.00	-0.90
25	ATOM	530	N	VAL	104	6.951	-7.865	2.786	1.00	-0.73
	ATOM	531	CA	VAL	104	5.938	-7.177	1.995	1.00	0.36
	ATOM	532	C	VAL	104	6.495	-6.965	0.560	1.00	0.57
	ATOM	533	O	VAL	104	7.691	-6.755	0.342	1.00	-0.57
	ATOM	534	CB	VAL	104	5.508	-5.847	2.653	1.00	0.00
30	ATOM	535	CG1	VAL	104	5.127	-6.067	4.123	1.00	0.00
	ATOM	536	CG2	VAL	104	6.564	-4.742	2.563	1.00	0.00
	ATOM	537	N	LEU	105	5.556	-7.029	-0.449	1.00	-0.73
	ATOM	538	CA	LEU	105	5.865	-6.735	-1.854	1.00	0.36
	ATOM	539	C	LEU	105	4.676	-5.946	-2.454	1.00	0.57
35	ATOM	540	O	LEU	105	3.525	-6.101	-2.047	1.00	-0.57
	ATOM	541	CB	LEU	105	5.992	-8.015	-2.715	1.00	0.00
	ATOM	542	CG	LEU	105	7.333	-8.772	-2.748	1.00	0.00
	ATOM	543	CD1	LEU	105	8.507	-7.866	-3.103	1.00	0.00
	ATOM	544	CD2	LEU	105	7.617	-9.584	-1.490	1.00	0.00
40	ATOM	545	N	VAL	106	4.987	-5.161	-3.537	1.00	-0.73
	ATOM	546	CA	VAL	106	3.968	-4.575	-4.414	1.00	0.36
	ATOM	547	C	VAL	106	4.187	-5.219	-5.797	1.00	0.57
	ATOM	548	O	VAL	106	5.312	-5.314	-6.300	1.00	-0.57
	ATOM	549	CB	VAL	106	4.148	-3.049	-4.505	1.00	0.00
45	ATOM	550	CG1	VAL	106	3.194	-2.393	-5.507	1.00	0.00
	ATOM	551	CG2	VAL	106	3.978	-2.391	-3.139	1.00	0.00
	ATOM	552	N	ALA	107	3.042	-5.637	-6.430	1.00	-0.73
	ATOM	553	CA	ALA	107	3.072	-6.236	-7.753	1.00	0.36
	ATOM	554	C	ALA	107	1.774	-5.927	-8.507	1.00	0.57
50	ATOM	555	O	ALA	107	0.702	-5.717	-7.943	1.00	-0.57
	ATOM	556	CB	ALA	107	3.257	-7.745	-7.658	1.00	0.00
	ATOM	557	N	GLU	108	1.909	-5.946	-9.874	1.00	-0.73

	ATOM	558	CA	GLU	108	0.787	-5.679	-10.757	1.00	0.36
	ATOM	559	C	GLU	108	0.416	-7.015	-11.447	1.00	0.57
	ATOM	560	O	GLU	108	1.255	-7.730	-11.997	1.00	-0.57
	ATOM	561	CB	GLU	108	1.155	-4.613	-11.788	1.00	0.00
5	ATOM	562	CG	GLU	108	1.600	-3.283	-11.179	1.00	-0.11
	ATOM	563	CD	GLU	108	1.850	-2.210	-12.230	1.00	0.91
	ATOM	564	OE1	GLU	108	2.073	-2.605	-13.412	1.00	-0.90
	ATOM	565	OE2	GLU	108	1.853	-1.011	-11.821	1.00	-0.90
	ATOM	566	N	SER	109	-0.915	-7.343	-11.405	1.00	-0.73
10	ATOM	567	CA	SER	109	-1.476	-8.564	-11.970	1.00	0.36
	ATOM	568	C	SER	109	-2.793	-8.227	-12.698	1.00	0.57
	ATOM	569	O	SER	109	-3.836	-7.978	-12.093	1.00	-0.57
	ATOM	570	CB	SER	109	-1.758	-9.617	-10.883	1.00	0.28
	ATOM	571	OG	SER	109	-2.479	-9.097	-9.758	1.00	-0.68
15	ATOM	572	N	THR	110	-2.684	-8.191	-14.076	1.00	-0.73
	ATOM	573	CA	THR	110	-3.883	-8.190	-14.960	1.00	0.36
	ATOM	574	C	THR	110	-4.633	-9.503	-14.625	1.00	0.57
	ATOM	575	O	THR	110	-4.018	-10.449	-14.114	1.00	-0.57
	ATOM	576	CB	THR	110	-3.399	-8.155	-16.436	1.00	0.28
20	ATOM	577	OG1	THR	110	-2.685	-6.937	-16.696	1.00	-0.68
	ATOM	578	CG2	THR	110	-4.443	-8.284	-17.532	1.00	0.00
	ATOM	579	N	PRO	111	-5.970	-9.639	-14.955	1.00	-0.66
	ATOM	580	CA	PRO	111	-6.751	-10.697	-14.295	1.00	0.36
	ATOM	581	C	PRO	111	-6.345	-12.183	-14.352	1.00	0.57
25	ATOM	582	O	PRO	111	-6.798	-12.979	-13.517	1.00	-0.57
	ATOM	583	CB	PRO	111	-8.154	-10.485	-14.853	1.00	0.00
	ATOM	584	CG	PRO	111	-8.242	-8.965	-14.896	1.00	0.00
	ATOM	585	CD	PRO	111	-6.859	-8.559	-15.383	1.00	0.30
	ATOM	586	N	PRO	112	-5.505	-12.636	-15.338	1.00	-0.66
30	ATOM	587	CA	PRO	112	-4.779	-13.906	-15.198	1.00	0.36
	ATOM	588	C	PRO	112	-3.696	-13.813	-14.084	1.00	0.57
	ATOM	589	O	PRO	112	-2.488	-13.855	-14.311	1.00	-0.57
	ATOM	590	CB	PRO	112	-4.159	-14.131	-16.587	1.00	0.00
	ATOM	591	CG	PRO	112	-4.999	-13.260	-17.514	1.00	0.00
35	ATOM	592	CD	PRO	112	-5.303	-12.054	-16.645	1.00	0.30
	ATOM	593	N	GLY	113	-4.219	-13.706	-12.813	1.00	-0.73
	ATOM	594	CA	GLY	113	-3.403	-13.552	-11.630	1.00	0.36
	ATOM	595	C	GLY	113	-2.926	-14.885	-11.040	1.00	0.57
	ATOM	596	O	GLY	113	-2.846	-15.931	-11.678	1.00	-0.57
40	ATOM	597	N	ASN	114	-2.501	-14.782	-9.729	1.00	-0.73
	ATOM	598	CA	ASN	114	-1.859	-15.910	-9.041	1.00	0.36
	ATOM	599	C	ASN	114	-2.301	-15.928	-7.569	1.00	0.57
	ATOM	600	O	ASN	114	-1.576	-16.274	-6.637	1.00	-0.57
	ATOM	601	CB	ASN	114	-0.343	-15.817	-9.172	1.00	0.06
45	ATOM	602	CG	ASN	114	0.332	-17.158	-8.998	1.00	0.57
	ATOM	603	OD1	ASN	114	0.759	-17.832	-9.930	1.00	-0.57
	ATOM	604	ND2	ASN	114	0.493	-17.583	-7.713	1.00	-0.80
	ATOM	605	N	ASP	115	-3.628	-15.684	-7.407	1.00	-0.73
	ATOM	606	CA	ASP	115	-4.344	-15.855	-6.162	1.00	0.36
50	ATOM	607	C	ASP	115	-5.518	-16.865	-6.403	1.00	0.57
	ATOM	608	O	ASP	115	-5.845	-17.226	-7.532	1.00	-0.57
	ATOM	609	CB	ASP	115	-4.676	-14.485	-5.609	1.00	-0.11

	ATOM	610	CG	ASP	115	-5.173	-13.310	-6.446	1.00	0.91
	ATOM	611	OD1	ASP	115	-5.010	-13.373	-7.688	1.00	-0.90
	ATOM	612	OD2	ASP	115	-5.552	-12.341	-5.682	1.00	-0.90
	ATOM	613	N	GLU	116	-6.178	-17.303	-5.264	1.00	-0.73
5	ATOM	614	CA	GLU	116	-7.407	-18.113	-5.319	1.00	0.36
	ATOM	615	C	GLU	116	-8.623	-17.365	-6.021	1.00	0.57
	ATOM	616	O	GLU	116	-9.458	-18.013	-6.667	1.00	-0.57
	ATOM	617	CB	GLU	116	-7.917	-18.515	-3.907	1.00	0.00
	ATOM	618	CG	GLU	116	-7.023	-19.412	-3.053	1.00	-0.11
10	ATOM	619	CD	GLU	116	-5.913	-18.713	-2.296	1.00	0.91
	ATOM	620	OE1	GLU	116	-5.794	-18.988	-1.061	1.00	-0.90
	ATOM	621	OE2	GLU	116	-5.123	-17.979	-2.948	1.00	-0.90
	ATOM	622	N	PRO	117	-8.827	-16.013	-5.736	1.00	-0.66
	ATOM	623	CA	PRO	117	-9.770	-15.160	-6.468	1.00	0.36
15	ATOM	624	C	PRO	117	-9.256	-14.844	-7.907	1.00	0.57
	ATOM	625	O	PRO	117	-8.296	-15.399	-8.434	1.00	-0.57
	ATOM	626	CB	PRO	117	-9.813	-13.858	-5.615	1.00	0.00
	ATOM	627	CG	PRO	117	-8.423	-13.761	-5.009	1.00	0.00
	ATOM	628	CD	PRO	117	-8.031	-15.213	-4.835	1.00	0.30
20	ATOM	629	N	TYR	118	-10.000	-13.892	-8.575	1.00	-0.73
	ATOM	630	CA	TYR	118	-9.483	-13.201	-9.759	1.00	0.36
	ATOM	631	C	TYR	118	-9.546	-11.689	-9.440	1.00	0.57
	ATOM	632	O	TYR	118	-10.397	-11.223	-8.679	1.00	-0.57
	ATOM	633	CB	TYR	118	-10.257	-13.586	-11.036	1.00	0.14
25	ATOM	634	CG	TYR	118	-11.702	-13.126	-11.105	1.00	-0.14
	ATOM	635	CD1	TYR	118	-12.077	-12.147	-12.035	1.00	-0.15
	ATOM	636	CD2	TYR	118	-12.684	-13.633	-10.240	1.00	-0.15
	ATOM	637	CE1	TYR	118	-13.373	-11.630	-12.043	1.00	-0.15
	ATOM	638	CE2	TYR	118	-13.978	-13.099	-10.236	1.00	-0.15
30	ATOM	639	CZ	TYR	118	-14.301	-12.071	-11.112	1.00	0.08
	ATOM	640	OH	TYR	118	-15.536	-11.493	-11.033	1.00	-0.53
	ATOM	641	N	THR	119	-8.596	-10.898	-10.047	1.00	-0.73
	ATOM	642	CA	THR	119	-8.747	-9.440	-10.073	1.00	0.36
	ATOM	643	C	THR	119	-9.629	-9.098	-11.293	1.00	0.57
35	ATOM	644	O	THR	119	-9.782	-9.868	-12.242	1.00	-0.57
	ATOM	645	CB	THR	119	-7.396	-8.689	-10.164	1.00	0.28
	ATOM	646	OG1	THR	119	-6.566	-9.255	-11.185	1.00	-0.68
	ATOM	647	CG2	THR	119	-6.634	-8.732	-8.843	1.00	0.00
	ATOM	648	N	GLU	120	-10.229	-7.861	-11.256	1.00	-0.73
40	ATOM	649	CA	GLU	120	-10.865	-7.276	-12.439	1.00	0.36
	ATOM	650	C	GLU	120	-10.011	-6.048	-12.785	1.00	0.57
	ATOM	651	O	GLU	120	-9.128	-5.645	-12.026	1.00	-0.57
	ATOM	652	CB	GLU	120	-12.318	-6.878	-12.162	1.00	0.00
	ATOM	653	CG	GLU	120	-13.199	-8.114	-12.026	1.00	-0.11
45	ATOM	654	CD	GLU	120	-14.694	-7.888	-11.819	1.00	0.91
	ATOM	655	OE1	GLU	120	-15.086	-6.689	-11.807	1.00	-0.90
	ATOM	656	OE2	GLU	120	-15.367	-8.960	-11.702	1.00	-0.90
	ATOM	657	N	GLN	121	-10.348	-5.372	-13.939	1.00	-0.73
	ATOM	658	CA	GLN	121	-9.462	-4.317	-14.461	1.00	0.36
50	ATOM	659	C	GLN	121	-9.203	-3.246	-13.374	1.00	0.57
	ATOM	660	O	GLN	121	-8.145	-2.625	-13.300	1.00	-0.57
	ATOM	661	CB	GLN	121	-10.123	-3.626	-15.670	1.00	0.00

	ATOM	662	CG	GLN	121	-9.755	-4.239	-17.020	1.00	0.06
	ATOM	663	CD	GLN	121	-9.889	-5.743	-17.055	1.00	0.57
	ATOM	664	OE1	GLN	121	-10.800	-6.358	-16.508	1.00	-0.57
	ATOM	665	NE2	GLN	121	-8.920	-6.384	-17.765	1.00	-0.80
5	ATOM	666	N	MET	122	-10.301	-2.980	-12.589	1.00	-0.73
	ATOM	667	CA	MET	122	-10.319	-2.004	-11.519	1.00	0.36
	ATOM	668	C	MET	122	-10.509	-2.603	-10.101	1.00	0.57
	ATOM	669	O	MET	122	-11.023	-1.941	-9.199	1.00	-0.57
	ATOM	670	CB	MET	122	-11.365	-0.907	-11.800	1.00	0.00
10	ATOM	671	CG	MET	122	-12.821	-1.396	-11.790	1.00	0.23
	ATOM	672	SD	MET	122	-13.306	-2.185	-13.367	1.00	-0.46
	ATOM	673	CE	MET	122	-14.492	-3.401	-12.722	1.00	0.23
	ATOM	674	N	GLY	123	-9.992	-3.858	-9.880	1.00	-0.73
	ATOM	675	CA	GLY	123	-10.013	-4.479	-8.555	1.00	0.36
15	ATOM	676	C	GLY	123	-8.630	-4.975	-8.114	1.00	0.57
	ATOM	677	O	GLY	123	-7.885	-5.549	-8.906	1.00	-0.57
	ATOM	678	N	ASN	124	-8.335	-4.749	-6.787	1.00	-0.73
	ATOM	679	CA	ASN	124	-7.002	-4.958	-6.198	1.00	0.36
	ATOM	680	C	ASN	124	-7.169	-5.714	-4.863	1.00	0.57
20	ATOM	681	O	ASN	124	-8.268	-5.844	-4.317	1.00	-0.57
	ATOM	682	CB	ASN	124	-6.342	-3.630	-5.853	1.00	0.06
	ATOM	683	CG	ASN	124	-6.192	-2.760	-7.060	1.00	0.57
	ATOM	684	OD1	ASN	124	-5.779	-3.175	-8.142	1.00	-0.57
	ATOM	685	ND2	ASN	124	-6.522	-1.456	-6.863	1.00	-0.80
25	ATOM	686	N	CYS	125	-5.997	-6.173	-4.287	1.00	-0.73
	ATOM	687	CA	CYS	125	-6.060	-7.176	-3.221	1.00	0.36
	ATOM	688	C	CYS	125	-4.725	-7.301	-2.434	1.00	0.57
	ATOM	689	O	CYS	125	-3.643	-6.910	-2.866	1.00	-0.57
	ATOM	690	CB	CYS	125	-6.520	-8.509	-3.857	1.00	0.05
30	ATOM	691	SG	CYS	125	-6.379	-10.039	-2.886	1.00	-1.05
	ATOM	692	N	GLY	126	-4.891	-7.951	-1.216	1.00	-0.73
	ATOM	693	CA	GLY	126	-3.791	-8.567	-0.486	1.00	0.36
	ATOM	694	C	GLY	126	-4.325	-9.614	0.518	1.00	0.57
	ATOM	695	O	GLY	126	-4.442	-9.388	1.721	1.00	-0.57
35	ATOM	696	N	GLU	127	-4.730	-10.819	-0.059	1.00	-0.73
	ATOM	697	CA	GLU	127	-5.575	-11.735	0.731	1.00	0.36
	ATOM	698	C	GLU	127	-4.873	-12.419	1.930	1.00	0.57
	ATOM	699	O	GLU	127	-5.506	-12.798	2.918	1.00	-0.57
	ATOM	700	CB	GLU	127	-6.287	-12.801	-0.136	1.00	0.00
40	ATOM	701	CG	GLU	127	-5.444	-13.968	-0.653	1.00	-0.11
	ATOM	702	CD	GLU	127	-4.371	-13.542	-1.628	1.00	0.91
	ATOM	703	OE1	GLU	127	-4.781	-12.919	-2.663	1.00	-0.90
	ATOM	704	OE2	GLU	127	-3.175	-13.799	-1.349	1.00	-0.90
	ATOM	705	N	LYS	128	-3.542	-12.726	1.765	1.00	-0.73
45	ATOM	706	CA	LYS	128	-2.769	-13.379	2.813	1.00	0.36
	ATOM	707	C	LYS	128	-1.276	-13.033	2.644	1.00	0.57
	ATOM	708	O	LYS	128	-0.645	-13.221	1.605	1.00	-0.57
	ATOM	709	CB	LYS	128	-2.989	-14.903	2.866	1.00	0.00
	ATOM	710	CG	LYS	128	-2.527	-15.611	1.593	1.00	0.00
50	ATOM	711	CD	LYS	128	-3.183	-16.971	1.371	1.00	0.00
	ATOM	712	CE	LYS	128	-2.913	-17.410	-0.062	1.00	0.50
	ATOM	713	NZ	LYS	128	-3.535	-18.706	-0.313	1.00	-0.85

	ATOM	714	N	GLY	129	-0.695	-12.487	3.774	1.00	-0.73
	ATOM	715	CA	GLY	129	0.554	-11.760	3.644	1.00	0.36
	ATOM	716	C	GLY	129	0.237	-10.326	3.204	1.00	0.57
	ATOM	717	O	GLY	129	-0.606	-10.059	2.349	1.00	-0.57
5	ATOM	718	N	GLU	130	0.980	-9.356	3.829	1.00	-0.73
	ATOM	719	CA	GLU	130	0.730	-7.928	3.583	1.00	0.36
	ATOM	720	C	GLU	130	1.478	-7.563	2.290	1.00	0.57
	ATOM	721	O	GLU	130	2.626	-7.083	2.274	1.00	-0.57
	ATOM	722	CB	GLU	130	1.195	-7.106	4.791	1.00	0.00
10	ATOM	723	CG	GLU	130	0.306	-7.372	6.005	1.00	-0.11
	ATOM	724	CD	GLU	130	0.786	-6.744	7.302	1.00	0.91
	ATOM	725	OE1	GLU	130	1.332	-5.605	7.228	1.00	-0.90
	ATOM	726	OE2	GLU	130	0.516	-7.400	8.346	1.00	-0.90
	ATOM	727	N	ARG	131	0.852	-7.963	1.133	1.00	-0.73
15	ATOM	728	CA	ARG	131	1.433	-7.779	-0.187	1.00	0.36
	ATOM	729	C	ARG	131	0.301	-7.389	-1.138	1.00	0.57
	ATOM	730	O	ARG	131	-0.835	-7.840	-1.014	1.00	-0.57
	ATOM	731	CB	ARG	131	2.137	-9.040	-0.719	1.00	0.00
	ATOM	732	CG	ARG	131	2.905	-9.781	0.369	1.00	0.00
20	ATOM	733	CD	ARG	131	3.859	-10.843	-0.146	1.00	0.33
	ATOM	734	NE	ARG	131	4.712	-11.291	0.963	1.00	-0.84
	ATOM	735	CZ	ARG	131	5.675	-12.208	0.912	1.00	1.20
	ATOM	736	NH1	ARG	131	6.007	-12.814	-0.230	1.00	-0.97
	ATOM	737	NH2	ARG	131	6.312	-12.545	2.032	1.00	-0.97
25	ATOM	738	N	ILE	132	0.667	-6.524	-2.141	1.00	-0.73
	ATOM	739	CA	ILE	132	-0.347	-5.811	-2.909	1.00	0.36
	ATOM	740	C	ILE	132	-0.409	-6.466	-4.311	1.00	0.57
	ATOM	741	O	ILE	132	0.548	-6.472	-5.087	1.00	-0.57
	ATOM	742	CB	ILE	132	-0.035	-4.299	-3.015	1.00	0.00
30	ATOM	743	CG1	ILE	132	0.471	-3.667	-1.697	1.00	0.00
	ATOM	744	CG2	ILE	132	-1.261	-3.538	-3.537	1.00	0.00
	ATOM	745	CD1	ILE	132	-0.457	-3.800	-0.500	1.00	0.00
	ATOM	746	N	HIS	133	-1.602	-7.097	-4.585	1.00	-0.73
	ATOM	747	CA	HIS	133	-2.019	-7.529	-5.926	1.00	0.36
35	ATOM	748	C	HIS	133	-2.793	-6.322	-6.538	1.00	0.57
	ATOM	749	O	HIS	133	-3.993	-6.148	-6.320	1.00	-0.57
	ATOM	750	CB	HIS	133	-2.951	-8.769	-5.851	1.00	0.18
	ATOM	751	C	HIS	133	-2.301	-10.043	-5.384	1.00	0.05
	ATOM	752	N1	HIS	133	-2.984	-10.960	-4.577	1.00	-0.57
40	ATOM	753	C1	HIS	133	-2.103	-11.918	-4.362	1.00	0.04
	ATOM	754	N2	HIS	133	-0.927	-11.704	-5.025	1.00	0.03
	ATOM	755	C2	HIS	133	-1.031	-10.510	-5.680	1.00	-0.30
	ATOM	756	N	LEU	134	-2.011	-5.395	-7.201	1.00	-0.73
	ATOM	757	CA	LEU	134	-2.556	-4.260	-8.007	1.00	0.36
45	ATOM	758	C	LEU	134	-2.785	-4.787	-9.453	1.00	0.57
	ATOM	759	O	LEU	134	-2.410	-5.918	-9.783	1.00	-0.57
	ATOM	760	CB	LEU	134	-1.507	-3.125	-7.963	1.00	0.00
	ATOM	761	CG	LEU	134	-1.838	-1.759	-8.601	1.00	0.00
	ATOM	762	CD1	LEU	134	-3.087	-1.109	-8.021	1.00	0.00
50	ATOM	763	CD2	LEU	134	-0.658	-0.802	-8.410	1.00	0.00
	ATOM	764	N	THR	135	-3.357	-3.938	-10.371	1.00	-0.73
	ATOM	765	CA	THR	135	-3.445	-4.268	-11.803	1.00	0.36

	ATOM	766	C	THR	135	-2.584	-3.275	-12.638	1.00	0.57
	ATOM	767	O	THR	135	-2.481	-2.082	-12.332	1.00	-0.57
	ATOM	768	CB	THR	135	-4.890	-4.275	-12.358	1.00	0.28
	ATOM	769	OG1	THR	135	-5.416	-2.949	-12.435	1.00	-0.68
5	ATOM	770	CG2	THR	135	-5.825	-5.135	-11.525	1.00	0.00
	ATOM	771	N	PRO	136	-2.006	-3.747	-13.806	1.00	-0.66
	ATOM	772	CA	PRO	136	-1.388	-2.840	-14.787	1.00	0.36
	ATOM	773	C	PRO	136	-2.444	-2.031	-15.570	1.00	0.57
	ATOM	774	O	PRO	136	-2.149	-1.075	-16.285	1.00	-0.57
10	ATOM	775	CB	PRO	136	-0.690	-3.766	-15.795	1.00	0.00
	ATOM	776	CG	PRO	136	-0.535	-5.086	-15.066	1.00	0.00
	ATOM	777	CD	PRO	136	-1.735	-5.127	-14.138	1.00	0.30
	ATOM	778	N	ASP	137	-3.714	-2.578	-15.512	1.00	-0.73
	ATOM	779	CA	ASP	137	-4.766	-2.217	-16.455	1.00	0.36
15	ATOM	780	C	ASP	137	-5.275	-0.776	-16.199	1.00	0.57
	ATOM	781	O	ASP	137	-5.968	-0.154	-17.010	1.00	-0.57
	ATOM	782	CB	ASP	137	-5.951	-3.170	-16.324	1.00	-0.11
	ATOM	783	CG	ASP	137	-5.648	-4.626	-16.635	1.00	0.91
	ATOM	784	OD1	ASP	137	-6.609	-5.293	-17.121	1.00	-0.90
20	ATOM	785	OD2	ASP	137	-4.497	-5.056	-16.333	1.00	-0.90
	ATOM	786	N	PHE	138	-4.977	-0.259	-14.956	1.00	-0.73
	ATOM	787	CA	PHE	138	-5.417	1.062	-14.556	1.00	0.36
	ATOM	788	C	PHE	138	-4.710	2.090	-15.454	1.00	0.57
	ATOM	789	O	PHE	138	-3.488	2.231	-15.504	1.00	-0.57
25	ATOM	790	CB	PHE	138	-5.013	1.451	-13.127	1.00	0.14
	ATOM	791	CG	PHE	138	-5.926	0.912	-12.064	1.00	-0.14
	ATOM	792	CD1	PHE	138	-7.200	1.457	-11.851	1.00	-0.15
	ATOM	793	CD2	PHE	138	-5.503	-0.146	-11.264	1.00	-0.15
	ATOM	794	CE1	PHE	138	-8.015	0.981	-10.824	1.00	-0.15
30	ATOM	795	CE2	PHE	138	-6.340	-0.650	-10.276	1.00	-0.15
	ATOM	796	CZ	PHE	138	-7.580	-0.071	-10.028	1.00	-0.15
	ATOM	797	N	ILE	139	-5.572	2.898	-16.182	1.00	-0.73
	ATOM	798	CA	ILE	139	-5.001	3.912	-17.071	1.00	0.36
	ATOM	799	C	ILE	139	-4.399	5.054	-16.194	1.00	0.57
35	ATOM	800	O	ILE	139	-5.016	6.070	-15.865	1.00	-0.57
	ATOM	801	CB	ILE	139	-6.019	4.471	-18.098	1.00	0.00
	ATOM	802	CG1	ILE	139	-7.368	4.903	-17.484	1.00	0.00
	ATOM	803	CG2	ILE	139	-6.237	3.446	-19.220	1.00	0.00
	ATOM	804	CD1	ILE	139	-8.191	5.768	-18.432	1.00	0.00
40	ATOM	805	N	ALA	140	-3.119	4.796	-15.740	1.00	-0.73
	ATOM	806	CA	ALA	140	-2.532	5.486	-14.595	1.00	0.36
	ATOM	807	C	ALA	140	-2.036	6.897	-14.981	1.00	0.57
	ATOM	808	O	ALA	140	-0.862	7.261	-14.976	1.00	-0.57
	ATOM	809	CB	ALA	140	-1.416	4.663	-13.970	1.00	0.00
45	ATOM	810	N	GLY	141	-3.061	7.767	-15.292	1.00	-0.73
	ATOM	811	CA	GLY	141	-2.816	9.129	-15.663	1.00	0.36
	ATOM	812	C	GLY	141	-2.513	10.000	-14.438	1.00	0.57
	ATOM	813	O	GLY	141	-2.660	9.662	-13.268	1.00	-0.57
	ATOM	814	N	LYS	142	-2.077	11.270	-14.760	1.00	-0.73
50	ATOM	815	CA	LYS	142	-1.541	12.158	-13.730	1.00	0.36
	ATOM	816	C	LYS	142	-2.579	13.134	-13.115	1.00	0.57
	ATOM	817	O	LYS	142	-2.216	14.027	-12.351	1.00	-0.57

	ATOM	818	CB	LYS	142	-0.362	12.962	-14.311	1.00	0.00
	ATOM	819	CG	LYS	142	0.801	12.065	-14.759	1.00	0.00
	ATOM	820	CD	LYS	142	1.971	12.847	-15.367	1.00	0.00
	ATOM	821	CE	LYS	142	1.624	13.472	-16.713	1.00	0.50
5	ATOM	822	NZ	LYS	142	2.840	14.082	-17.302	1.00	-0.85
	ATOM	823	N	LYS	143	-3.882	12.936	-13.507	1.00	-0.73
	ATOM	824	CA	LYS	143	-5.078	13.611	-12.966	1.00	0.36
	ATOM	825	C	LYS	143	-6.143	13.675	-14.081	1.00	0.57
	ATOM	826	O	LYS	143	-7.345	13.707	-13.837	1.00	-0.57
10	ATOM	827	CB	LYS	143	-4.881	15.047	-12.446	1.00	0.00
	ATOM	828	CG	LYS	143	-4.670	15.117	-10.925	1.00	0.00
	ATOM	829	CD	LYS	143	-5.992	15.034	-10.149	1.00	0.00
	ATOM	830	CE	LYS	143	-5.813	15.020	-8.636	1.00	0.50
	ATOM	831	NZ	LYS	143	-5.190	16.263	-8.160	1.00	-0.85
15	ATOM	832	N	LEU	144	-5.629	13.839	-15.363	1.00	-0.73
	ATOM	833	CA	LEU	144	-6.539	14.162	-16.472	1.00	0.36
	ATOM	834	C	LEU	144	-7.448	12.958	-16.807	1.00	0.57
	ATOM	835	O	LEU	144	-8.552	13.082	-17.325	1.00	-0.57
	ATOM	836	CB	LEU	144	-5.799	14.658	-17.728	1.00	0.00
20	ATOM	837	CG	LEU	144	-4.949	13.637	-18.521	1.00	0.00
	ATOM	838	CD1	LEU	144	-4.529	14.254	-19.861	1.00	0.00
	ATOM	839	CD2	LEU	144	-3.702	13.174	-17.769	1.00	0.00
	ATOM	840	N	ALA	145	-6.847	11.729	-16.594	1.00	-0.73
	ATOM	841	CA	ALA	145	-7.676	10.544	-16.453	1.00	0.36
25	ATOM	842	C	ALA	145	-7.809	10.313	-14.936	1.00	0.57
	ATOM	843	O	ALA	145	-6.914	10.623	-14.146	1.00	-0.57
	ATOM	844	CB	ALA	145	-7.024	9.332	-17.095	1.00	0.00
	ATOM	845	N	GLU	146	-8.958	9.648	-14.554	1.00	-0.73
	ATOM	846	CA	GLU	146	-9.336	9.618	-13.136	1.00	0.36
30	ATOM	847	C	GLU	146	-8.305	8.849	-12.280	1.00	0.57
	ATOM	848	O	GLU	146	-8.081	9.127	-11.100	1.00	-0.57
	ATOM	849	CB	GLU	146	-10.701	8.913	-12.993	1.00	0.00
	ATOM	850	CG	GLU	146	-11.859	9.908	-12.927	1.00	-0.11
	ATOM	851	CD	GLU	146	-11.968	10.634	-11.596	1.00	0.91
35	ATOM	852	OE1	GLU	146	-11.378	10.115	-10.607	1.00	-0.90
	ATOM	853	OE2	GLU	146	-12.680	11.682	-11.599	1.00	-0.90
	ATOM	854	N	TYR	147	-7.799	7.724	-12.878	1.00	-0.73
	ATOM	855	CA	TYR	147	-7.143	6.634	-12.158	1.00	0.36
	ATOM	856	C	TYR	147	-5.641	6.861	-11.930	1.00	0.57
40	ATOM	857	O	TYR	147	-4.813	5.961	-12.032	1.00	-0.57
	ATOM	858	CB	TYR	147	-7.391	5.283	-12.845	1.00	0.14
	ATOM	859	CG	TYR	147	-8.855	4.907	-12.779	1.00	-0.14
	ATOM	860	CD1	TYR	147	-9.686	5.067	-13.896	1.00	-0.15
	ATOM	861	CD2	TYR	147	-9.402	4.428	-11.579	1.00	-0.15
45	ATOM	862	CE1	TYR	147	-11.047	4.769	-13.808	1.00	-0.15
	ATOM	863	CE2	TYR	147	-10.760	4.132	-11.493	1.00	-0.15
	ATOM	864	CZ	TYR	147	-11.572	4.310	-12.605	1.00	0.08
	ATOM	865	OH	TYR	147	-12.896	4.019	-12.474	1.00	-0.53
	ATOM	866	N	GLY	148	-5.314	8.092	-11.396	1.00	-0.73
50	ATOM	867	CA	GLY	148	-3.987	8.309	-10.845	1.00	0.36
	ATOM	868	C	GLY	148	-3.921	7.601	-9.486	1.00	0.57
	ATOM	869	O	GLY	148	-4.676	7.921	-8.558	1.00	-0.57

	ATOM	870	N	PRO	149	-3.050	6.546	-9.340	1.00	-0.66
	ATOM	871	CA	PRO	149	-3.351	5.465	-8.396	1.00	0.36
	ATOM	872	C	PRO	149	-2.915	5.739	-6.952	1.00	0.57
	ATOM	873	O	PRO	149	-2.793	4.826	-6.143	1.00	-0.57
5	ATOM	874	CB	PRO	149	-2.580	4.254	-8.945	1.00	0.00
	ATOM	875	CG	PRO	149	-1.388	4.908	-9.633	1.00	0.00
	ATOM	876	CD	PRO	149	-2.029	6.119	-10.288	1.00	0.30
	ATOM	877	N	GLN	150	-2.755	7.055	-6.580	1.00	-0.73
	ATOM	878	CA	GLN	150	-2.458	7.373	-5.186	1.00	0.36
10	ATOM	879	C	GLN	150	-3.759	7.502	-4.371	1.00	0.57
	ATOM	880	O	GLN	150	-3.936	6.901	-3.317	1.00	-0.57
	ATOM	881	CB	GLN	150	-1.636	8.664	-5.103	1.00	0.00
	ATOM	882	CG	GLN	150	-1.084	8.911	-3.696	1.00	0.06
	ATOM	883	CD	GLN	150	-0.525	10.309	-3.543	1.00	0.57
15	ATOM	884	OE1	GLN	150	-0.724	11.234	-4.323	1.00	-0.57
	ATOM	885	NE2	GLN	150	0.233	10.500	-2.430	1.00	-0.80
	ATOM	886	N	GLY	151	-4.647	8.450	-4.825	1.00	-0.73
	ATOM	887	CA	GLY	151	-5.822	8.799	-4.048	1.00	0.36
	ATOM	888	C	GLY	151	-7.071	8.044	-4.488	1.00	0.57
20	ATOM	889	O	GLY	151	-8.133	8.644	-4.658	1.00	-0.57
	ATOM	890	N	LYS	152	-6.911	6.681	-4.619	1.00	-0.73
	ATOM	891	CA	LYS	152	-8.050	5.807	-4.923	1.00	0.36
	ATOM	892	C	LYS	152	-7.655	4.335	-4.981	1.00	0.57
	ATOM	893	O	LYS	152	-8.458	3.459	-4.687	1.00	-0.57
25	ATOM	894	CB	LYS	152	-8.750	6.146	-6.244	1.00	0.00
	ATOM	895	CG	LYS	152	-7.810	6.348	-7.442	1.00	0.00
	ATOM	896	CD	LYS	152	-8.124	7.649	-8.168	1.00	0.00
	ATOM	897	CE	LYS	152	-9.515	7.683	-8.791	1.00	0.50
	ATOM	898	NZ	LYS	152	-9.807	9.082	-9.095	1.00	-0.85
30	ATOM	899	N	ALA	153	-6.418	4.079	-5.554	1.00	-0.73
	ATOM	900	CA	ALA	153	-5.776	2.826	-5.155	1.00	0.36
	ATOM	901	C	ALA	153	-4.914	3.261	-3.950	1.00	0.57
	ATOM	902	O	ALA	153	-5.435	3.788	-2.956	1.00	-0.57
	ATOM	903	CB	ALA	153	-5.063	2.171	-6.325	1.00	0.00
35	ATOM	904	N	PHE	154	-3.551	3.374	-4.098	1.00	-0.73
	ATOM	905	CA	PHE	154	-2.641	2.863	-3.070	1.00	0.36
	ATOM	906	C	PHE	154	-2.926	3.215	-1.595	1.00	0.57
	ATOM	907	O	PHE	154	-2.465	2.537	-0.674	1.00	-0.57
	ATOM	908	CB	PHE	154	-1.220	3.410	-3.315	1.00	0.14
40	ATOM	909	CG	PHE	154	-0.412	2.748	-4.406	1.00	-0.14
	ATOM	910	CD1	PHE	154	0.032	1.430	-4.252	1.00	-0.15
	ATOM	911	CD2	PHE	154	-0.042	3.455	-5.558	1.00	-0.15
	ATOM	912	CE1	PHE	154	0.828	0.835	-5.231	1.00	-0.15
	ATOM	913	CE2	PHE	154	0.740	2.853	-6.545	1.00	-0.15
45	ATOM	914	CZ	PHE	154	1.182	1.545	-6.376	1.00	-0.15
	ATOM	915	N	VAL	155	-3.543	4.420	-1.343	1.00	-0.73
	ATOM	916	CA	VAL	155	-3.933	4.730	0.030	1.00	0.36
	ATOM	917	C	VAL	155	-5.041	3.765	0.518	1.00	0.57
	ATOM	918	O	VAL	155	-5.102	3.438	1.704	1.00	-0.57
50	ATOM	919	CB	VAL	155	-4.356	6.203	0.180	1.00	0.00
	ATOM	920	CG1	VAL	155	-4.799	6.513	1.614	1.00	0.00
	ATOM	921	CG2	VAL	155	-3.193	7.139	-0.161	1.00	0.00

	ATOM	922	N	HIS	156	-5.965	3.371	-0.416	1.00	-0.73
	ATOM	923	CA	HIS	156	-7.024	2.377	-0.148	1.00	0.36
	ATOM	924	C	HIS	156	-6.318	1.029	0.189	1.00	0.57
	ATOM	925	O	HIS	156	-6.637	0.333	1.163	1.00	-0.57
5	ATOM	926	CB	HIS	156	-7.957	2.312	-1.356	1.00	0.17
	ATOM	927	C	HIS	156	-9.225	1.625	-1.068	1.00	-0.02
	ATOM	928	N1	HIS	156	-10.157	1.265	-2.008	1.00	-1.30
	ATOM	929	C1	HIS	156	-11.195	0.660	-1.349	1.00	0.14
	ATOM	930	N2	HIS	156	-11.053	0.545	-0.028	1.00	-0.28
10	ATOM	931	C2	HIS	156	-9.804	1.095	0.141	1.00	-0.01
	ATOM	932	N	GLU	157	-5.281	0.648	-0.635	1.00	-0.73
	ATOM	933	CA	GLU	157	-4.667	-0.669	-0.489	1.00	0.36
	ATOM	934	C	GLU	157	-3.845	-0.660	0.803	1.00	0.57
	ATOM	935	O	GLU	157	-3.903	-1.579	1.617	1.00	-0.57
15	ATOM	936	CB	GLU	157	-3.740	-1.053	-1.652	1.00	0.00
	ATOM	937	CG	GLU	157	-4.514	-1.536	-2.880	1.00	-0.11
	ATOM	938	CD	GLU	157	-5.273	-0.419	-3.565	1.00	0.91
	ATOM	939	OE1	GLU	157	-6.075	-0.764	-4.463	1.00	-0.90
	ATOM	940	OE2	GLU	157	-4.996	0.753	-3.178	1.00	-0.90
20	ATOM	941	N	TRP	158	-2.994	0.405	0.982	1.00	-0.73
	ATOM	942	CA	TRP	158	-2.187	0.501	2.190	1.00	0.36
	ATOM	943	C	TRP	158	-3.008	0.928	3.427	1.00	0.57
	ATOM	944	O	TRP	158	-2.527	0.916	4.563	1.00	-0.57
	ATOM	945	CB	TRP	158	-0.946	1.390	2.021	1.00	0.18
25	ATOM	946	CG	TRP	158	0.117	0.704	1.205	1.00	-0.18
	ATOM	947	CD1	TRP	158	0.295	0.789	-0.161	1.00	-0.30
	ATOM	948	CD2	TRP	158	1.106	-0.213	1.689	1.00	0.00
	ATOM	949	NE1	TRP	158	1.289	-0.076	-0.522	1.00	0.03
	ATOM	950	CE2	TRP	158	1.780	-0.727	0.584	1.00	-0.15
30	ATOM	951	CE3	TRP	158	1.468	-0.685	2.964	1.00	-0.15
	ATOM	952	CZ2	TRP	158	2.754	-1.729	0.688	1.00	-0.15
	ATOM	953	CZ3	TRP	158	2.448	-1.675	3.091	1.00	-0.15
	ATOM	954	CH2	TRP	158	3.072	-2.198	1.964	1.00	-0.15
	ATOM	955	N	ALA	159	-4.324	1.266	3.234	1.00	-0.73
35	ATOM	956	CA	ALA	159	-5.227	1.389	4.360	1.00	0.36
	ATOM	957	C	ALA	159	-5.568	-0.046	4.802	1.00	0.57
	ATOM	958	O	ALA	159	-5.510	-0.399	5.984	1.00	-0.57
	ATOM	959	CB	ALA	159	-6.490	2.176	4.064	1.00	0.00
	ATOM	960	N	HIS	160	-5.984	-0.920	3.831	1.00	-0.73
40	ATOM	961	CA	HIS	160	-6.401	-2.274	4.186	1.00	0.36
	ATOM	962	C	HIS	160	-5.236	-3.221	4.480	1.00	0.57
	ATOM	963	O	HIS	160	-5.253	-3.954	5.464	1.00	-0.57
	ATOM	964	CB	HIS	160	-7.271	-2.949	3.124	1.00	0.18
	ATOM	965	CG	HIS	160	-8.551	-2.235	2.939	1.00	-0.33
45	ATOM	966	ND1	HIS	160	-9.463	-2.000	3.928	1.00	0.03
	ATOM	967	CD2	HIS	160	-9.040	-1.645	1.801	1.00	0.08
	ATOM	968	CE1	HIS	160	-10.417	-1.235	3.327	1.00	0.04
	ATOM	969	NE2	HIS	160	-10.255	-1.086	2.026	1.00	-0.57
	ATOM	970	N	LEU	161	-4.284	-3.314	3.514	1.00	-0.73
50	ATOM	971	CA	LEU	161	-3.443	-4.490	3.302	1.00	0.36
	ATOM	972	C	LEU	161	-2.067	-4.346	3.982	1.00	0.57
	ATOM	973	O	LEU	161	-1.006	-4.576	3.404	1.00	-0.57

	ATOM	974	CB	LEU	161	-3.274	-4.718	1.796	1.00	0.00
	ATOM	975	CG	LEU	161	-4.589	-4.713	0.994	1.00	0.00
	ATOM	976	CD1	LEU	161	-4.267	-4.768	-0.490	1.00	0.00
	ATOM	977	CD2	LEU	161	-5.536	-5.829	1.426	1.00	0.00
5	ATOM	978	N	ARG	162	-2.143	-4.036	5.318	1.00	-0.73
	ATOM	979	CA	ARG	162	-0.992	-3.563	6.088	1.00	0.36
	ATOM	980	C	ARG	162	-1.357	-3.788	7.576	1.00	0.57
	ATOM	981	O	ARG	162	-2.523	-3.784	7.978	1.00	-0.57
	ATOM	982	CB	ARG	162	-0.753	-2.094	5.705	1.00	0.00
10	ATOM	983	CG	ARG	162	0.140	-1.237	6.616	1.00	0.00
	ATOM	984	CD	ARG	162	-0.335	0.223	6.628	1.00	0.33
	ATOM	985	NE	ARG	162	-1.775	0.327	6.909	1.00	-0.84
	ATOM	986	CZ	ARG	162	-2.386	-0.262	7.938	1.00	1.20
	ATOM	987	NH1	ARG	162	-1.733	-0.598	9.039	1.00	-0.97
15	ATOM	988	NH2	ARG	162	-3.682	-0.538	7.879	1.00	-0.97
	ATOM	989	N	TRP	163	-0.283	-3.910	8.430	1.00	-0.73
	ATOM	990	CA	TRP	163	-0.424	-4.477	9.783	1.00	0.36
	ATOM	991	C	TRP	163	-1.468	-3.695	10.606	1.00	0.57
	ATOM	992	O	TRP	163	-1.378	-2.495	10.876	1.00	-0.57
20	ATOM	993	CB	TRP	163	0.926	-4.415	10.522	1.00	0.18
	ATOM	994	CG	TRP	163	0.856	-4.832	11.963	1.00	-0.18
	ATOM	995	CD1	TRP	163	1.053	-4.024	13.069	1.00	-0.30
	ATOM	996	CD2	TRP	163	0.606	-6.154	12.454	1.00	0.00
	ATOM	997	NE1	TRP	163	0.928	-4.799	14.193	1.00	0.03
25	ATOM	998	CE2	TRP	163	0.625	-6.093	13.846	1.00	-0.15
	ATOM	999	CE3	TRP	163	0.390	-7.405	11.842	1.00	-0.15
	ATOM	1000	CZ2	TRP	163	0.418	-7.213	14.658	1.00	-0.15
	ATOM	1001	CZ3	TRP	163	0.190	-8.538	12.638	1.00	-0.15
	ATOM	1002	CH2	TRP	163	0.199	-8.440	14.026	1.00	-0.15
30	ATOM	1003	N	GLY	164	-2.583	-4.417	10.980	1.00	-0.73
	ATOM	1004	CA	GLY	164	-3.727	-3.746	11.564	1.00	0.36
	ATOM	1005	C	GLY	164	-4.541	-3.077	10.453	1.00	0.57
	ATOM	1006	O	GLY	164	-4.304	-1.941	10.037	1.00	-0.57
	ATOM	1007	N	VAL	165	-5.500	-3.895	9.898	1.00	-0.73
35	ATOM	1008	CA	VAL	165	-6.197	-3.515	8.667	1.00	0.36
	ATOM	1009	C	VAL	165	-7.250	-2.439	9.016	1.00	0.57
	ATOM	1010	O	VAL	165	-7.829	-2.427	10.105	1.00	-0.57
	ATOM	1011	CB	VAL	165	-6.872	-4.724	7.973	1.00	0.00
	ATOM	1012	CG1	VAL	165	-5.869	-5.856	7.702	1.00	0.00
40	ATOM	1013	CG2	VAL	165	-8.066	-5.295	8.747	1.00	0.00
	ATOM	1014	N	PHE	166	-7.532	-1.536	8.018	1.00	-0.73
	ATOM	1015	CA	PHE	166	-8.670	-0.622	8.120	1.00	0.36
	ATOM	1016	C	PHE	166	-9.874	-1.186	7.348	1.00	0.57
	ATOM	1017	O	PHE	166	-9.771	-2.065	6.496	1.00	-0.57
45	ATOM	1018	CB	PHE	166	-8.348	0.788	7.616	1.00	0.14
	ATOM	1019	CG	PHE	166	-7.530	1.551	8.627	1.00	-0.14
	ATOM	1020	CD1	PHE	166	-8.150	2.089	9.757	1.00	-0.15
	ATOM	1021	CD2	PHE	166	-6.141	1.650	8.505	1.00	-0.15
	ATOM	1022	CE1	PHE	166	-7.386	2.671	10.762	1.00	-0.15
50	ATOM	1023	CE2	PHE	166	-5.374	2.198	9.528	1.00	-0.15
	ATOM	1024	CZ	PHE	166	-5.998	2.696	10.662	1.00	-0.15
	ATOM	1025	N	ASP	167	-11.070	-0.608	7.695	1.00	-0.73

	ATOM	1026	CA	ASP	167	-12.379	-1.138	7.309	1.00	0.36
	ATOM	1027	C	ASP	167	-12.842	-0.443	6.010	1.00	0.57
	ATOM	1028	O	ASP	167	-12.260	0.534	5.529	1.00	-0.57
	ATOM	1029	CB	ASP	167	-13.439	-0.884	8.380	1.00	-0.11
5	ATOM	1030	CG	ASP	167	-12.867	-1.127	9.739	1.00	0.91
	ATOM	1031	OD1	ASP	167	-13.206	-2.166	10.370	1.00	-0.90
	ATOM	1032	OD2	ASP	167	-12.021	-0.283	10.181	1.00	-0.90
	ATOM	1033	N	GLU	168	-13.975	-0.990	5.424	1.00	-0.73
	ATOM	1034	CA	GLU	168	-14.753	-0.178	4.489	1.00	0.36
10	ATOM	1035	C	GLU	168	-15.725	0.685	5.344	1.00	0.57
	ATOM	1036	O	GLU	168	-15.896	0.517	6.551	1.00	-0.57
	ATOM	1037	CB	GLU	168	-15.594	-1.024	3.502	1.00	0.00
	ATOM	1038	CG	GLU	168	-14.862	-2.199	2.835	1.00	-0.11
	ATOM	1039	CD	GLU	168	-13.747	-1.826	1.903	1.00	0.91
15	ATOM	1040	OE1	GLU	168	-13.002	-2.706	1.388	1.00	-0.90
	ATOM	1041	OE2	GLU	168	-13.419	-0.647	1.614	1.00	-0.90
	ATOM	1042	N	TYR	169	-16.431	1.621	4.636	1.00	-0.73
	ATOM	1043	CA	TYR	169	-17.284	2.629	5.263	1.00	0.36
	ATOM	1044	C	TYR	169	-18.298	3.072	4.179	1.00	0.57
20	ATOM	1045	O	TYR	169	-18.420	2.478	3.105	1.00	-0.57
	ATOM	1046	CB	TYR	169	-16.422	3.788	5.796	1.00	0.14
	ATOM	1047	CG	TYR	169	-17.049	4.592	6.912	1.00	-0.14
	ATOM	1048	CD1	TYR	169	-17.330	3.988	8.147	1.00	-0.15
	ATOM	1049	CD2	TYR	169	-17.326	5.956	6.740	1.00	-0.15
25	ATOM	1050	CE1	TYR	169	-17.894	4.728	9.188	1.00	-0.15
	ATOM	1051	CE2	TYR	169	-17.894	6.693	7.780	1.00	-0.15
	ATOM	1052	CZ	TYR	169	-18.170	6.076	8.994	1.00	0.08
	ATOM	1053	OH	TYR	169	-18.713	6.842	9.982	1.00	-0.53
	ATOM	1054	N	ASN	170	-19.131	4.121	4.496	1.00	-0.73
30	ATOM	1055	CA	ASN	170	-20.255	4.494	3.622	1.00	0.36
	ATOM	1056	C	ASN	170	-20.494	6.016	3.728	1.00	0.57
	ATOM	1057	O	ASN	170	-21.603	6.529	3.855	1.00	-0.57
	ATOM	1058	CB	ASN	170	-21.500	3.663	3.949	1.00	0.06
	ATOM	1059	CG	ASN	170	-21.891	2.749	2.808	1.00	0.57
35	ATOM	1060	OD1	ASN	170	-22.969	2.831	2.226	1.00	-0.57
	ATOM	1061	ND2	ASN	170	-21.004	1.766	2.491	1.00	-0.80
	ATOM	1062	N	ASN	171	-19.351	6.776	3.571	1.00	-0.73
	ATOM	1063	CA	ASN	171	-19.393	8.238	3.396	1.00	0.36
	ATOM	1064	C	ASN	171	-18.011	8.671	2.832	1.00	0.57
40	ATOM	1065	O	ASN	171	-17.013	7.962	2.966	1.00	-0.57
	ATOM	1066	CB	ASN	171	-19.723	8.909	4.723	1.00	0.06
	ATOM	1067	CG	ASN	171	-19.753	10.413	4.700	1.00	0.57
	ATOM	1068	OD1	ASN	171	-19.114	11.071	5.524	1.00	-0.57
	ATOM	1069	ND2	ASN	171	-20.561	11.010	3.787	1.00	-0.80
45	ATOM	1070	N	ASP	172	-17.978	9.897	2.197	1.00	-0.73
	ATOM	1071	CA	ASP	172	-17.227	9.998	0.930	1.00	0.36
	ATOM	1072	C	ASP	172	-15.716	10.261	1.021	1.00	0.57
	ATOM	1073	O	ASP	172	-14.916	9.680	0.284	1.00	-0.57
	ATOM	1074	CB	ASP	172	-17.814	11.112	0.057	1.00	-0.11
50	ATOM	1075	CG	ASP	172	-19.152	10.542	-0.367	1.00	0.91
	ATOM	1076	OD1	ASP	172	-19.209	10.139	-1.560	1.00	-0.90
	ATOM	1077	OD2	ASP	172	-20.008	10.489	0.573	1.00	-0.90

	ATOM	1078	N	GLU	173	-15.304	11.299	1.818	1.00	-0.73
	ATOM	1079	CA	GLU	173	-13.973	11.902	1.689	1.00	0.36
	ATOM	1080	C	GLU	173	-12.855	11.173	2.482	1.00	0.57
	ATOM	1081	O	GLU	173	-11.811	11.721	2.833	1.00	-0.57
5	ATOM	1082	CB	GLU	173	-14.018	13.421	1.961	1.00	0.00
	ATOM	1083	CG	GLU	173	-13.990	13.874	3.424	1.00	-0.11
	ATOM	1084	CD	GLU	173	-14.927	13.179	4.378	1.00	0.91
	ATOM	1085	OE1	GLU	173	-15.994	12.675	3.927	1.00	-0.90
	ATOM	1086	OE2	GLU	173	-14.529	13.053	5.576	1.00	-0.90
10	ATOM	1087	N	LYS	174	-13.077	9.832	2.688	1.00	-0.73
	ATOM	1088	CA	LYS	174	-12.115	8.932	3.302	1.00	0.36
	ATOM	1089	C	LYS	174	-11.877	7.776	2.316	1.00	0.57
	ATOM	1090	O	LYS	174	-12.727	7.422	1.503	1.00	-0.57
	ATOM	1091	CB	LYS	174	-12.524	8.415	4.696	1.00	0.00
15	ATOM	1092	CG	LYS	174	-14.025	8.393	5.033	1.00	0.00
	ATOM	1093	CD	LYS	174	-14.559	9.778	5.412	1.00	0.00
	ATOM	1094	CE	LYS	174	-16.019	9.767	5.830	1.00	0.50
	ATOM	1095	NZ	LYS	174	-16.538	11.139	5.826	1.00	-0.85
	ATOM	1096	N	PHE	175	-10.650	7.168	2.425	1.00	-0.73
20	ATOM	1097	CA	PHE	175	-10.249	6.072	1.524	1.00	0.36
	ATOM	1098	C	PHE	175	-10.647	4.748	2.190	1.00	0.57
	ATOM	1099	O	PHE	175	-9.828	3.923	2.572	1.00	-0.57
	ATOM	1100	CB	PHE	175	-8.744	6.100	1.235	1.00	0.14
	ATOM	1101	CG	PHE	175	-8.297	7.439	0.695	1.00	-0.14
25	ATOM	1102	CD1	PHE	175	-8.509	7.776	-0.646	1.00	-0.15
	ATOM	1103	CD2	PHE	175	-7.736	8.389	1.561	1.00	-0.15
	ATOM	1104	CE1	PHE	175	-8.174	9.049	-1.104	1.00	-0.15
	ATOM	1105	CE2	PHE	175	-7.394	9.656	1.099	1.00	-0.15
	ATOM	1106	CZ	PHE	175	-7.612	9.985	-0.235	1.00	-0.15
30	ATOM	1107	N	TYR	176	-12.011	4.643	2.374	1.00	-0.73
	ATOM	1108	CA	TYR	176	-12.637	3.503	3.029	1.00	0.36
	ATOM	1109	C	TYR	176	-13.936	3.142	2.274	1.00	0.57
	ATOM	1110	O	TYR	176	-14.875	2.580	2.830	1.00	-0.57
	ATOM	1111	CB	TYR	176	-13.012	3.806	4.499	1.00	0.14
35	ATOM	1112	CG	TYR	176	-11.939	4.134	5.515	1.00	-0.14
	ATOM	1113	CD1	TYR	176	-10.656	3.580	5.472	1.00	-0.15
	ATOM	1114	CD2	TYR	176	-12.274	4.942	6.612	1.00	-0.15
	ATOM	1115	CE1	TYR	176	-9.703	3.893	6.446	1.00	-0.15
	ATOM	1116	CE2	TYR	176	-11.338	5.214	7.610	1.00	-0.15
40	ATOM	1117	CZ	TYR	176	-10.059	4.689	7.523	1.00	0.08
	ATOM	1118	OH	TYR	176	-9.182	4.960	8.533	1.00	-0.53
	ATOM	1119	N	LEU	177	-13.977	3.405	0.928	1.00	-0.73
	ATOM	1120	CA	LEU	177	-15.112	2.984	0.117	1.00	0.36
	ATOM	1121	C	LEU	177	-14.725	3.058	-1.365	1.00	0.57
45	ATOM	1122	O	LEU	177	-13.706	3.625	-1.756	1.00	-0.57
	ATOM	1123	CB	LEU	177	-16.402	3.789	0.387	1.00	0.00
	ATOM	1124	CG	LEU	177	-16.481	5.203	-0.232	1.00	0.00
	ATOM	1125	CD1	LEU	177	-17.870	5.799	0.006	1.00	0.00
	ATOM	1126	CD2	LEU	177	-15.413	6.148	0.309	1.00	0.00
50	ATOM	1127	N	SER	178	-15.640	2.506	-2.231	1.00	-0.73
	ATOM	1128	CA	SER	178	-15.373	2.410	-3.673	1.00	0.36
	ATOM	1129	C	SER	178	-15.571	3.780	-4.369	1.00	0.57

	ATOM	1130	O	SER	178	-16.416	3.979	-5.242	1.00	-0.57
	ATOM	1131	CB	SER	178	-16.316	1.376	-4.309	1.00	0.28
	ATOM	1132	OG	SER	178	-16.177	0.111	-3.648	1.00	-0.68
	ATOM	1133	N	ASN	179	-14.703	4.766	-3.970	1.00	-0.73
5	ATOM	1134	CA	ASN	179	-14.758	6.154	-4.442	1.00	0.36
	ATOM	1135	C	ASN	179	-13.323	6.723	-4.336	1.00	0.57
	ATOM	1136	O	ASN	179	-12.447	6.207	-3.643	1.00	-0.57
	ATOM	1137	CB	ASN	179	-15.745	6.972	-3.603	1.00	0.06
	ATOM	1138	CG	ASN	179	-16.098	8.308	-4.223	1.00	0.57
10	ATOM	1139	OD1	ASN	179	-15.567	8.758	-5.237	1.00	-0.57
	ATOM	1140	ND2	ASN	179	-17.038	9.022	-3.546	1.00	-0.80
	ATOM	1141	N	GLY	180	-13.075	7.860	-5.078	1.00	-0.73
	ATOM	1142	CA	GLY	180	-11.823	8.563	-4.894	1.00	0.36
	ATOM	1143	C	GLY	180	-11.610	9.626	-5.970	1.00	0.57
15	ATOM	1144	O	GLY	180	-10.562	9.764	-6.607	1.00	-0.57
	ATOM	1145	N	ARG	181	-12.650	10.522	-6.105	1.00	-0.73
	ATOM	1146	CA	ARG	181	-12.522	11.723	-6.935	1.00	0.36
	ATOM	1147	C	ARG	181	-11.928	12.880	-6.088	1.00	0.57
	ATOM	1148	O	ARG	181	-12.347	14.034	-6.119	1.00	-0.57
20	ATOM	1149	CB	ARG	181	-13.862	12.123	-7.557	1.00	0.00
	ATOM	1150	CG	ARG	181	-14.565	10.953	-8.255	1.00	0.00
	ATOM	1151	CD	ARG	181	-15.596	11.438	-9.269	1.00	0.33
	ATOM	1152	NE	ARG	181	-14.923	11.965	-10.454	1.00	-0.84
	ATOM	1153	CZ	ARG	181	-15.458	12.630	-11.472	1.00	1.20
25	ATOM	1154	NH1	ARG	181	-16.761	12.909	-11.530	1.00	-0.97
	ATOM	1155	NH2	ARG	181	-14.664	13.021	-12.465	1.00	-0.97
	ATOM	1156	N	ILE	182	-10.817	12.525	-5.349	1.00	-0.73
	ATOM	1157	CA	ILE	182	-10.180	13.455	-4.427	1.00	0.36
	ATOM	1158	C	ILE	182	-9.191	14.368	-5.196	1.00	0.57
30	ATOM	1159	O	ILE	182	-8.569	14.006	-6.197	1.00	-0.57
	ATOM	1160	CB	ILE	182	-9.496	12.654	-3.286	1.00	0.00
	ATOM	1161	CG1	ILE	182	-9.494	13.405	-1.940	1.00	0.00
	ATOM	1162	CG2	ILE	182	-8.073	12.211	-3.654	1.00	0.00
	ATOM	1163	CD1	ILE	182	-10.872	13.479	-1.293	1.00	0.00
35	ATOM	1164	N	GLN	183	-8.967	15.604	-4.612	1.00	-0.73
	ATOM	1165	CA	GLN	183	-8.019	16.538	-5.218	1.00	0.36
	ATOM	1166	C	GLN	183	-6.582	16.113	-4.837	1.00	0.57
	ATOM	1167	O	GLN	183	-5.657	16.142	-5.654	1.00	-0.57
	ATOM	1168	CB	GLN	183	-8.291	17.986	-4.788	1.00	0.00
40	ATOM	1169	CG	GLN	183	-7.346	19.002	-5.441	1.00	0.06
	ATOM	1170	CD	GLN	183	-7.434	18.972	-6.953	1.00	0.57
	ATOM	1171	OE1	GLN	183	-6.677	18.307	-7.659	1.00	-0.57
	ATOM	1172	NE2	GLN	183	-8.480	19.656	-7.487	1.00	-0.80
	ATOM	1173	N	ALA	184	-6.386	15.836	-3.509	1.00	-0.73
45	ATOM	1174	CA	ALA	184	-5.100	15.393	-2.977	1.00	0.36
	ATOM	1175	C	ALA	184	-5.383	14.480	-1.772	1.00	0.57
	ATOM	1176	O	ALA	184	-6.519	14.344	-1.316	1.00	-0.57
	ATOM	1177	CB	ALA	184	-4.244	16.589	-2.590	1.00	0.00
	ATOM	1178	N	VAL	185	-4.295	13.807	-1.267	1.00	-0.73
50	ATOM	1179	CA	VAL	185	-4.445	12.956	-0.087	1.00	0.36
	ATOM	1180	C	VAL	185	-4.353	13.875	1.149	1.00	0.57
	ATOM	1181	O	VAL	185	-3.504	14.758	1.258	1.00	-0.57

	ATOM	1182	CB VAL	185	-3.335	11.882	-0.019	1.00	0.00
	ATOM	1183	CG1 VAL	185	-3.497	10.956	1.192	1.00	0.00
	ATOM	1184	CG2 VAL	185	-3.306	11.030	-1.291	1.00	0.00
	ATOM	1185	N ARG	186	-5.251	13.576	2.142	1.00	-0.73
5	ATOM	1186	CA ARG	186	-5.152	14.135	3.475	1.00	0.36
	ATOM	1187	C ARG	186	-5.910	13.161	4.391	1.00	0.57
	ATOM	1188	O ARG	186	-6.786	12.404	3.975	1.00	-0.57
	ATOM	1189	CB ARG	186	-5.793	15.529	3.590	1.00	0.00
	ATOM	1190	CG ARG	186	-5.076	16.403	4.631	1.00	0.00
10	ATOM	1191	CD ARG	186	-5.996	17.424	5.300	1.00	0.33
	ATOM	1192	NE ARG	186	-6.855	16.787	6.309	1.00	-0.84
	ATOM	1193	CZ ARG	186	-7.425	17.400	7.357	1.00	1.20
	ATOM	1194	NH1 ARG	186	-7.338	18.717	7.545	1.00	-0.97
	ATOM	1195	NH2 ARG	186	-8.096	16.671	8.248	1.00	-0.97
15	ATOM	1196	N CYS	187	-5.610	13.275	5.733	1.00	-0.73
	ATOM	1197	CA CYS	187	-6.373	12.467	6.682	1.00	0.36
	ATOM	1198	C CYS	187	-7.739	13.172	6.785	1.00	0.57
	ATOM	1199	O CYS	187	-7.830	14.376	7.059	1.00	-0.57
	ATOM	1200	CB CYS	187	-5.761	12.453	8.087	1.00	0.23
20	ATOM	1201	SG CYS	187	-4.017	11.935	8.077	1.00	-0.41
	ATOM	1202	N SER	188	-8.848	12.397	6.555	1.00	-0.73
	ATOM	1203	CA SER	188	-10.179	12.898	6.894	1.00	0.36
	ATOM	1204	C SER	188	-10.282	12.926	8.438	1.00	0.57
	ATOM	1205	O SER	188	-9.469	12.374	9.180	1.00	-0.57
25	ATOM	1206	CB SER	188	-11.312	12.034	6.317	1.00	0.28
	ATOM	1207	OG SER	188	-12.557	12.336	6.950	1.00	-0.68
	ATOM	1208	N ALA	189	-11.403	13.580	8.918	1.00	-0.73
	ATOM	1209	CA ALA	189	-11.798	13.392	10.311	1.00	0.36
	ATOM	1210	C ALA	189	-12.176	11.921	10.572	1.00	0.57
30	ATOM	1211	O ALA	189	-12.065	11.403	11.679	1.00	-0.57
	ATOM	1212	CB ALA	189	-12.983	14.283	10.648	1.00	0.00
	ATOM	1213	N GLY	190	-12.679	11.228	9.496	1.00	-0.73
	ATOM	1214	CA GLY	190	-13.096	9.846	9.619	1.00	0.36
	ATOM	1215	C GLY	190	-11.948	8.831	9.659	1.00	0.57
35	ATOM	1216	O GLY	190	-12.181	7.638	9.822	1.00	-0.57
	ATOM	1217	N ILE	191	-10.675	9.328	9.444	1.00	-0.73
	ATOM	1218	CA ILE	191	-9.491	8.475	9.614	1.00	0.36
	ATOM	1219	C ILE	191	-8.973	8.525	11.078	1.00	0.57
	ATOM	1220	O ILE	191	-8.190	7.676	11.515	1.00	-0.57
40	ATOM	1221	CB ILE	191	-8.410	8.811	8.542	1.00	0.00
	ATOM	1222	CG1 ILE	191	-8.950	8.417	7.142	1.00	0.00
	ATOM	1223	CG2 ILE	191	-7.063	8.133	8.824	1.00	0.00
	ATOM	1224	CD1 ILE	191	-7.955	8.493	5.993	1.00	0.00
	ATOM	1225	N THR	192	-9.358	9.604	11.863	1.00	-0.73
45	ATOM	1226	CA THR	192	-9.242	9.422	13.317	1.00	0.36
	ATOM	1227	C THR	192	-10.476	8.605	13.757	1.00	0.57
	ATOM	1228	O THR	192	-11.364	8.262	12.974	1.00	-0.57
	ATOM	1229	CB THR	192	-9.034	10.707	14.138	1.00	0.28
	ATOM	1230	OG1 THR	192	-8.730	10.340	15.495	1.00	-0.68
50	ATOM	1231	CG2 THR	192	-10.204	11.677	14.147	1.00	0.00
	ATOM	1232	N GLY	193	-10.467	8.169	15.058	1.00	-0.73
	ATOM	1233	CA GLY	193	-11.538	7.332	15.566	1.00	0.36

	ATOM	1234	C	GLY	193	-11.291	5.874	15.171	1.00	0.57
	ATOM	1235	O	GLY	193	-11.033	5.005	16.005	1.00	-0.57
	ATOM	1236	N	THR	194	-11.287	5.603	13.822	1.00	-0.73
	ATOM	1237	CA	THR	194	-10.957	4.267	13.316	1.00	0.36
5	ATOM	1238	C	THR	194	-9.541	3.884	13.791	1.00	0.57
	ATOM	1239	O	THR	194	-9.232	2.733	14.098	1.00	-0.57
	ATOM	1240	CB	THR	194	-10.990	4.181	11.781	1.00	0.28
	ATOM	1241	OG1	THR	194	-10.125	5.184	11.237	1.00	-0.68
	ATOM	1242	CG2	THR	194	-12.395	4.367	11.227	1.00	0.00
10	ATOM	1243	N	ASN	195	-8.628	4.925	13.833	1.00	-0.73
	ATOM	1244	CA	ASN	195	-7.247	4.667	14.237	1.00	0.36
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 Thr His Asn Gln Glu Ala Pro Asn Leu Gln Asn Gln Val Cys Ser Leu
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 35 40 45
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 Phe Glu Ala Thr Gly Lys Arg Phe Tyr Phe Lys Asn Val Ala Ile Leu
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 85 90 95
 Glu Thr Phe Lys Asn Ala Asp Val Leu Val Ser Thr Thr Ser Pro Leu
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 115 120 125
 Gly Ile Arg Ile His Leu Thr Pro Asp Phe Leu Ala Gly Lys Lys Leu
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Thr Gln Tyr Gly Pro Gln Asp Arg Thr Phe Val His Glu Trp Ala His
 145 150 155 160
 Phe Arg Trp Gly Val Phe Asn Glu Tyr Asn Asn Asp Glu Lys Phe Tyr
 165 170 175
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 195 200 205
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 210 215 220
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 Ser Tyr Asp Gln Ala Asp Val Ile Val Ala Asp Pro His Leu Gln His
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 Ser Arg Lys Asn Thr Val Glu Ala Thr Arg Cys Ser Thr Asp Ile Thr
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 55 Gly Thr Ser Val Val Arg Glu Cys Gln Gly Gly Ser Cys Val Ser Arg
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 Arg Cys Arg Arg Asp Ala Lys Thr Gly Met Gln Glu Ala Lys Cys Thr
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 Glu Thr Tyr Lys Asn Ala Asp Val Val Val Thr Glu Pro Asn Pro Pro
 100 105 110
 35 Glu Asn Asp Gly Pro Tyr Thr Glu Gln Met Gly Asn Cys Gly Glu Lys
 115 120 125
 Gly Glu Lys Ile Tyr Phe Thr Pro Asp Phe Val Ala Gly Lys Lys Val
 130 135 140
 Leu Gln Tyr Gly Pro Gln Gly Arg Val Phe Val His Glu Trp Ala His
 145 150 155 160
 40 Leu Arg Trp Gly Val Phe Asn Glu Tyr Asn Asn Glu Gln Lys Phe Tyr
 165 170 175
 Leu Ser Asn Lys Lys Glu Gln Pro Val Ile Cys Ser Ala Ala Ile Arg
 180 185 190
 45 Gly Thr Asn Val Leu Pro Gln Cys Gln Gly Gly Ser Cys Val Thr Lys
 195 200 205
 Pro Cys Arg Ala Asp Arg Val Thr Gly Leu Phe Gln Lys Glu Cys Glu
 210 215 220
 Phe Ile Pro Asp Pro Gln Gln Ser Glu Lys Ala Ser Ile Met Phe Ala
 225 230 235 240
 50 Gln Ser Ile Asp Thr Val Val Glu Phe Cys Lys Glu Lys Asn His Asn
 245 250 255
 Lys Glu Ala Pro Asn Asp Gln Asn Gln Lys Cys Asn Leu Arg Ser Thr
 260 265 270
 55 Trp Glu Val Ile Gln Asp Ser Glu Asp Phe Lys Lys Thr Thr Pro Met
 275 280 285
 Thr Thr Gln Pro Pro Ala Pro Thr Phe Ser Leu Leu Gln Ile Gly Gln
 290 295 300

Arg Ile
305

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5  <210> 12
   <211> 308
   <212> PRT
   <213> Bos taurus

10 <400> 12
   Met Val Pro Arg Leu Thr Val Ile Leu Phe Leu Thr Leu His Leu Leu
   1      5      10      15
   Pro Gly Met Lys Ser Ser Met Val Asn Leu Ile Asn Asn Gly Tyr Asp
   20      25      30
15  Gly Ile Val Ile Ala Ile Asn Pro Ser Val Pro Glu Asp Glu Lys Leu
   35      40      45
   Ile Gln Asn Ile Lys Glu Met Val Thr Glu Ala Ser Thr Tyr Leu Phe
   50      55      60
   His Ala Thr Lys Arg Arg Val Tyr Phe Arg Asn Val Ser Ile Leu Ile
   65      70      75      80
20  Pro Met Thr Trp Lys Ser Lys Ser Glu Tyr Leu Met Pro Lys Gln Glu
   85      90      95
   Ser Tyr Asp Gln Ala Glu Val Ile Val Ala Asn Pro Tyr Leu Lys His
   100     105     110
25  Gly Asp Asp Pro Tyr Thr Leu Gln Tyr Gly Arg Cys Gly Glu Lys Gly
   115     120     125
   Gln Tyr Ile His Phe Thr Pro Asn Phe Leu Leu Thr Asn Asn Leu Pro
   130     135     140
   Ile Tyr Gly Ser Arg Gly Arg Ala Phe Val His Glu Trp Ala His Leu
   145     150     155     160
30  Arg Trp Gly Ile Phe Asp Glu Tyr Asn Gly Asp Gln Pro Phe Tyr Ile
   165     170     175
   Ser Arg Arg Asn Thr Ile Glu Ala Thr Arg Cys Ser Thr His Ile Thr
   180     185     190
35  Gly Thr Asn Val Ile Val Lys Cys Gln Gly Gly Ser Cys Ile Thr Arg
   195     200     205
   Pro Cys Arg Arg Asp Ser Gln Thr Gly Leu Tyr Glu Ala Lys Cys Thr
   210     215     220
   Phe Ile Pro Glu Lys Ser Gln Thr Ala Arg Glu Ser Ile Met Phe Met
   225     230     235     240
40  Gln Ser Leu His Ser Val Thr Glu Phe Cys Thr Glu Lys Thr His Asn
   245     250     255
   Val Glu Ala Pro Asn Leu Gln Asn Lys Met Cys Asn Gly Lys Ser Thr
   260     265     270
45  Trp Asp Val Ile Met Asn Ser Thr Asp Phe Gln Asn Thr Ser Pro Met
   275     280     285
   Thr Glu Met Asn Pro Pro Thr Gln Pro Thr Phe Ser Leu Leu Lys Ser
   290     295     300
   Lys Gln Arg Val
50  305

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<210> 13
 <211> 247
 <212> PRT
 <213> Ciona intestinalis

5

<400> 13
 Glu Ser Thr Thr Leu Leu Asn Ser Ile Lys Ala Ala Trp Thr Glu Ala
 1 5 10 15
 Ser Ala Ala Leu Tyr Thr Ala Thr Arg Lys Arg Ala Tyr Phe Gly Asn
 20 25 30
 Ile Thr Ile Leu Val Pro Lys Ser Trp Asn Gly Thr Tyr Lys Arg Ala
 35 40 45
 Phe Asp Glu Thr Tyr Asp Ala Ala Asp Val Val Val Thr Asn Thr Asn
 50 55 60
 Arg Val Arg Gly Asn Ile Pro Tyr Val Leu Gln Pro Gly Gly Cys Gly
 65 70 75 80
 Glu Pro Gly Thr Arg Ile Phe Thr Thr Arg Asp Tyr Tyr Thr Asn Asp
 85 90 95
 Thr Tyr Val Glu Ser Phe Gly Gln Arg Gly Lys Val Met Val His Glu
 100 105 110
 Trp Ser His Tyr Arg Trp Gly Val Phe Asp Glu Ile Ala Ser Gly Asp
 115 120 125
 Tyr Ala Pro Phe Tyr Ile Ser Ser Thr Gly Thr Ile Glu Ala Thr Arg
 130 135 140
 Cys Ser Leu Gly Ile Gln Gly Glu Asn Met Ile Val Gln Asn Asn Glu
 145 150 155 160
 Ile Val Gln Asp Val Cys Asn Tyr Asp Pro Gln Thr Leu Leu Pro Asn
 165 170 175
 Ser Thr Asp Cys Lys Phe Ile Leu Ala Trp Asp Gln Asp Leu Asp Leu
 180 185 190
 Lys Ala Ser Ile Met Ser Tyr Gln Tyr Val Asn Glu Ile Asn Gly Phe
 195 200 205
 Cys Asp Asp Asn Asp Asn Asp Pro Leu Asn Arg His Asn Arg Glu Ala
 210 215 220
 Pro Asn Glu His Asn Asp Lys Cys Asn Lys Arg Ser Val Trp Asp Val
 225 230 235 240
 Ile Thr Ser Ser Val Asp Phe
 245

40

<210> 14
 <211> 274
 <212> PRT
 <213> Ciona intestinalis

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<220>
 <221> MISC_FEATURE
 <222> (49)..(49)
 <223> any natural amino acid residue
 <220>
 <221> MISC_FEATURE
 <222> (263)..(263)
 <223> any natural amino acid residue

50

55

<400> 14
 Asn Pro Ala Val Pro Glu Asp Pro Asn Leu Val Ser Ala Ile Gln Ser
 1 5 10 15
 Ser Trp Ile Glu Ala Ser Gly Asp Leu Tyr Thr Ala Thr Arg Gln Arg
 20 25 30

Ser Tyr Phe Gly Glu Ile Thr Ile Leu Ile Pro Lys Thr Trp Ser Lys
 35 40 45
 Xaa Lys Leu Val Ile Asn Gly Ser Glu Ser Tyr Glu Thr Ala Asp Val
 50 55 60
 5 Leu Ile Ala Glu Ala Asn Pro Val Tyr Gln Asp Thr Pro Tyr Thr Leu
 65 70 75 80
 Gln Tyr Gly Asn Cys Gly Glu Thr Ala Ser Tyr Ile His Leu Thr Pro
 85 90 95
 10 Asp Tyr Leu Thr Asn Gln Ser Phe Val Glu Asp Phe Gly Pro Arg Gly
 100 105 110
 Lys Ala Ile Val His Glu Trp Ala His Leu Arg Trp Gly Val Phe Asp
 115 120 125
 Glu Thr Tyr Thr Thr Gly Tyr Ser Pro Tyr Tyr Tyr Asp Ser His Gly
 130 135 140
 15 Thr Val Gln Ala Thr Arg Cys Pro Ser Thr Leu Asp Gly Lys Asn Lys
 145 150 155 160
 Val Val Asp Tyr Ser Thr Gly Asn Ser Arg Asp Cys Gln Arg Asn Leu
 165 170 175
 20 Glu Asn Gly Leu Met Glu Asp Gly Cys Leu Phe Leu Pro Tyr Ala Glu
 180 185 190
 Gln Ser Ala Asp Leu Thr Thr Ser Leu Met Ser His Gln Tyr Leu Ser
 195 200 205
 Gln Val Thr Met Phe Cys His Asn Asp Glu Thr Asp Ser Tyr Asn His
 210 215 220
 25 His Asn Arg Glu Ala Pro Asn Glu Gln Asn Arg Leu Cys Asp Leu Lys
 225 230 235 240
 Ser Ala Trp Glu Val Ile Met Glu Ser Lys Asp Phe Leu Asn Asn Ala
 245 250 255
 30 Asn Pro Arg Asn Met Val Xaa Asn Thr Asn Pro Ile Phe Arg Leu Val
 260 265 270
 Gln Ile

 <210> 15
 35 <211> 282
 <212> PRT
 <213> Ciona intestinalis

 <400> 15
 40 Val Thr Leu Val Asn Asn Gly Tyr Asp Gly Ile Val Val Ala Ile Asn
 1 5 10 15
 Pro Ala Val Ala Glu Asp Glu Thr Leu Ile Asn Lys Ile Arg Asn Met
 20 25 30
 Phe Thr Arg Ala Ser Pro Thr Leu Phe Thr Ala Thr Lys Lys Arg Ala
 35 40 45
 45 Tyr Phe Arg Asn Ile Asn Ile Leu Val Pro Lys Thr Trp Thr Ser Gly
 50 55 60
 Ser Tyr Gln Thr Ala Val Gly Leu Thr Tyr Arg Lys Ala Asp Val Ile
 65 70 75 80
 50 Ile Ala Pro Pro Asn Pro Val Arg Gly Asp Asn Pro Tyr Val Leu Gln
 85 90 95
 Thr Gly Ala Cys Gly Glu Pro Gly Thr His Met His Leu Thr Pro Glu
 100 105 110
 Trp Val Asn Asp Thr Arg Glu Ser Val Tyr Gly Pro Ser Asp Lys Ala
 115 120 125
 55 Ile Val His Glu Trp Ala His Leu Arg Trp Gly Val Phe Asp Glu Tyr
 130 135 140

Ala Thr Gly Asp His Lys Arg His Tyr Leu Asp Ser Asn Asn Val Leu
 145 150 155 160
 Gln Gly Thr Arg Cys Pro Leu Ser Ile Arg Gly Val Asn Arg Glu Tyr
 165 170 175
 5 Val Pro Pro Tyr Gln Val Leu Asn Gln Thr Cys Ile Ile Asn Gln Thr
 180 185 190
 Thr Leu Leu Pro Ala Ser Asp Thr Cys His Phe Ile Pro Gly Ile Glu
 195 200 205
 Gln Pro Arg Gly Leu Lys Thr Ser Met Met Phe Tyr Ser Tyr Leu Ser
 210 215 220
 10 Ser Val Ile Glu Phe Cys His Ser Asp Pro Ser Asp Pro Val Asn Gln
 225 230 235 240
 His Asn Thr Glu Ala Asp Asn Glu Gln Asn Ala Lys Cys Asn Leu Arg
 245 250 255
 15 Ser Thr Trp Asp Val Ile Thr Ser Thr Ser Asp Phe Ser Gly Gly Ser
 260 265 270
 Asn Pro Pro Asn Pro Thr Leu Thr Asn Leu
 275 280

 20
 <210> 16
 <211> 286
 <212> PRT
 <213> Ciona intestinalis

 25
 <400> 16
 Ser Glu Val Asn Leu Val Asn Asn Gly Tyr Glu Gly Ile Val Val Ala
 1 5 10 15
 Ile Asn Pro Ser Ile Pro Glu Asp Ala Ser Leu Val Asp Asn Ile Lys
 20 25 30
 30 Thr Leu Leu Asn Glu Ala Ser Pro Ile Leu Trp Ser Ala Thr Lys Asn
 35 40 45
 Arg Ala Tyr Phe Gly Glu Val Thr Ile Leu Val Pro Ser Thr Trp Thr
 50 55 60
 35 Gly Ser Tyr Thr Gln Ala Thr His Gly Gln Val Tyr Asn Lys Ala Asp
 65 70 75 80
 Ile Ile Val Ala Asp Pro Asn Pro Gln Tyr Met Asp Thr Pro Tyr Thr
 85 90 95
 Ile Gln Tyr Gln Gln Cys Gly Asp Pro Gly Glu Tyr Ile His Leu Thr
 100 105 110
 40 Pro Asn Phe Leu Ser Gln Ala Gly Tyr Glu Gln Asn Tyr Gly Asn Lys
 115 120 125
 Gly Lys Ala Leu Val His Glu Trp Ala His Leu Arg Trp Gly Val Tyr
 130 135 140
 45 Asp Glu Tyr Ala Ser Glu Gly Tyr Ala Pro Phe Tyr Tyr Ser Asn Arg
 145 150 155 160
 Gly Gly Gly Gln Pro Tyr Met Glu Ala Thr Arg Cys Pro Leu Ala Leu
 165 170 175
 Gly Gly Val Thr Arg Tyr Pro Asn Pro Ala Asn Gly Asn Gln Leu Glu
 180 185 190
 50 His Cys Thr Ser Asp Pro Asn Asn Phe Leu Pro Leu Glu Gly Cys
 195 200 205
 Leu Phe Phe Pro Phe Ser Glu Leu Gly Gln Pro Asp Asp Leu Ser Ala
 210 215 220
 55 Ser Leu Leu Ser His Gln Phe Val Asp Gln Val Val Asp Phe Cys His
 225 230 235 240
 Asn Asp Thr Asn Asp Pro Thr Asn Leu His Asn Lys Glu Ala Pro Asn
 245 250 255

Glu His Asn Arg Leu Cys Asp Gln Arg Ser Val Trp Glu Ile Met Met
 260 265 270
 Ala Ser Arg Asp Phe Asn Ala Val Asn His Pro Asn Pro Thr
 275 280 285

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<210> 17
 <211> 273
 <212> PRT
 10 <213> Ciona intestinalis
 <220>
 <221> MISC_FEATURE
 <222> (267)..(267)
 <223> any natural amino acid residue

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<400> 17
 Val Thr Leu Val Gly Asn Lys Tyr Lys Gly Ile Val Val Ala Ile Asn
 1 5 10 15
 Pro Ser Ile Pro Glu Asp Gln Asp Leu Ile Asn Asn Ile Lys Ala Leu
 20 20 25 30
 Leu Asn Glu Ala Ser Pro Ile Leu Trp Ser Ala Thr Lys Asn Arg Ala
 35 40 45
 Tyr Phe Gly Glu Val Thr Ile Leu Val Pro Ser Thr Trp Thr Gly Ser
 50 55 60
 25 Tyr Thr Gln Ala Thr His Gly Gln Val Tyr Asn Lys Ala Asp Ile Ile
 65 70 75 80
 Val Ala Asp Pro Asn Pro Gln Tyr Met Asp Thr Pro Tyr Thr Ile Gln
 85 90 95
 Tyr Gln Gln Cys Gly Asp Pro Gly Glu Tyr Ile His Leu Thr Pro Asn
 30 100 105 110
 Phe Ile Asn Glu Lys Asn Asp Phe Val Glu Asn Tyr Gly Ser Lys Gly
 115 120 125
 Lys Ala Leu Val His Glu Trp Ala His Leu Arg Trp Gly Ile Tyr Asp
 130 135 140
 35 Glu Tyr Ala Ser Glu Gly Tyr Asp Pro Phe Tyr Tyr Ser Ser Thr Gln
 145 150 155 160
 Tyr Val Gln Pro Thr Leu Glu Ala Thr Arg Cys Pro Leu Ser Val Ala
 165 170 175
 Gly Met Met Leu Tyr Leu Asp Pro Leu Ser Gly Lys Phe Glu Phe Cys
 40 180 185 190
 Thr Ser Asn Pro Glu Asn Asn Phe Leu Pro Glu Glu Gly Cys Ile Phe
 195 200 205
 Phe Pro Arg Ser Lys Glu Gly Gln Pro Ala Asp Leu Ile Tyr Ser Phe
 210 215 220
 45 Ser Leu Thr Gln Val Val Asp Phe Cys His Asn Asp Thr Asn Asp Pro
 225 230 235 240
 Thr Asn Leu His Asn Lys Glu Ala Pro Asn Glu His Asn Arg Leu Cys
 245 250 255
 Asp Gln Arg Ser Val Trp Glu Val Met Asn Xaa Ser Ser Asp Phe Lys
 50 260 265 270
 Gln

55

<210> 18
 <211> 279
 <212> PRT
 <213> Ciona intestinalis

<400> 18
 Val Lys Leu Gln Ser Asn Gly Tyr Asp Gly Val Leu Val Ala Ile Asn
 1 5 10 15
 Pro Ala Val Pro Glu Asn Glu Thr Leu Ile Arg Asn Ile Arg Ala Ser
 5 20 25 30
 Ile Asp Leu Ile Gly Ala Thr Ser His Ser Leu Phe Ile Leu Thr
 35 40 45
 Lys Lys Arg Ala Tyr Phe Arg Asn Ile Asn Ile Leu Val Pro Lys Thr
 50 55 60
 10 Trp Thr Gly Ala Arg Tyr Asp Thr Ala Ile Gly Leu Ser Tyr Arg Lys
 65 70 75 80
 Ala Asp Val Ile Val Ala Pro Ala Asn Ser Ala Lys Gly Asn Asn Pro
 85 90 95
 Tyr Thr Arg Gln Thr Gly Gly Cys Gly Asp Pro Gly Thr Tyr Ile His
 15 100 105 110
 Ile Thr Pro Glu Tyr Val Tyr Asn Pro Gln Glu His Leu Tyr Gly Pro
 115 120 125
 Arg Gly Lys Lys Ala Ile Val His Glu Trp Ser His Leu Arg Trp Gly
 130 135 140
 20 Val Phe Asp Glu Tyr Ala Thr Gly Asn His Lys Arg His Tyr Ile Asp
 145 150 155 160
 Ser Asn Asn Ile Leu Gln Ala Thr Arg Cys Pro Leu Ser Leu Arg Gly
 165 170 175
 Met Asn Ile Glu Tyr Ala Pro Pro Tyr Asn Thr Arg Cys Ala Val Asn
 25 180 185 190
 Arg Ser Ser Leu Leu Pro Leu Thr Glu Asn Cys Tyr Phe Phe Pro Ala
 195 200 205
 Ser Arg Gln Pro Arg Gly Leu Asn Ser Ser Met Met Ser Phe Ser Tyr
 210 215 220
 30 Leu His Ser Val Glu Ala Phe Cys His Asn Asp Pro Asn Glu Pro Ile
 225 230 235 240
 Asn Phe His Asn Ser Glu Ala Asp Asn Glu Gln Asn Ala Lys Cys Asn
 245 250 255
 Leu Lys Ser Leu Trp Glu Val Ile Gly Ala Ser Pro Asp Phe Arg Glu
 35 260 265 270
 Gly Ala Asn Pro Pro Asn Pro
 275

40 <210> 19
 <211> 241
 <212> PRT
 <213> Danio rerio

45 <400> 19
 Ser Val Phe Val Val Leu Trp Met Leu Leu Pro Tyr Pro Phe Thr Gly
 1 5 10 15
 Ile Lys Leu Asp Gly Gly Gly Tyr Val Asp Ile Ser Ile Ala Ile Gly
 20 25 30
 50 Ala Lys Val Lys Gln Asp Asp Thr Leu Ile Asp Lys Ile Lys Glu Met
 35 40 45
 Val Thr Asp Gly Ser Phe Tyr Leu Tyr His Ala Leu Asp Lys Lys Val
 50 55 60
 Tyr Leu Lys Asp Ala Thr Ile Leu Val Pro Ser Gln Trp Ser Cys Lys
 55 65 70 75 80
 Ser Cys Ser Ile Ala Arg Thr Glu Leu Phe Glu Lys Ala Gln Ile Lys
 85 90 95

Ile Asp His Ala Lys Leu Met Glu Pro Arg Thr Lys Leu Tyr Gly Glu
 100 105 110
 Cys Gly Val Gly Gly Glu Tyr Ile His Phe Thr Pro Asp Phe Leu Leu
 115 120 125
 5 Asn Asp Ser Ala Ile Gln Met Tyr Gly Pro Arg Gly Lys Val Phe Leu
 130 135 140
 His Glu Trp Ala His Leu Arg Trp Gly Val Tyr Asp Glu Tyr Asn Glu
 145 150 155 160
 10 Glu Lys Pro Phe Tyr Leu Ser Asn Gly Arg Val Glu Tyr Thr Arg Cys
 165 170 175
 Thr Thr Asn Ile Glu Gly Gln Cys Phe Glu Ile Asn Gly Gly Ser Leu
 180 185 190
 Gln Ser Cys Arg Ile Asn Pro Glu Thr Phe Leu Pro Ser Ser Asp Cys
 195 200 205
 15 Glu Leu Ser Pro Asn Lys Asp Gln Asn Thr Asp Ser Ser Val Met Cys
 210 215 220
 Ser Pro Ser Leu Gln Ser Leu Thr Thr Phe Cys Arg Glu Thr Glu His
 225 230 235 240
 Asn

20

<210> 20
 <211> 268
 <212> PRT
 25 <213> Gallus gallus
 <220>
 <221> MISC_FEATURE
 <222> (39)..(39)
 <223> any natural amino acid residue
 30 <220>
 <221> MISC_FEATURE
 <222> (61)..(61)
 <223> any natural amino acid residue
 <220>
 35 <221> MISC_FEATURE
 <222> (65)..(65)
 <223> any natural amino acid residue
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 <221> MISC_FEATURE
 40 <222> (77)..(77)
 <223> any natural amino acid residue
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 <222> (168)..(168)
 45 <223> any natural amino acid residue
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 <222> (171)..(171)
 <223> any natural amino acid residue
 50 <220>
 <221> MISC_FEATURE
 <222> (172)..(172)
 <223> any natural amino acid residue
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 55 <221> MISC_FEATURE
 <222> (197)..(197)
 <223> any natural amino acid residue

<400> 20
 Met Gly Val Phe Arg Ser Leu Ile Phe Leu Leu Ser Phe Gln Leu Leu
 1 5 10 15
 His Val Ala Lys Gly Ser Met Val Lys Leu Asn Glu Ser Gly Tyr Glu
 20 25 30
 5 Asp Leu Val Val Cys Asn Xaa Ser Gln Arg Asp Arg Arg Cys Gln His
 35 40 45
 His Pro Glu His Lys Gly Asn Asp Gln Arg Cys Phe Xaa Leu Phe Val
 50 55 60
 10 Xaa Ser Tyr Lys Thr Ser Ile Phe Leu Gln Ala Leu Xaa Arg Ile Ile
 65 70 75 80
 Leu Pro Lys Thr Trp Lys Lys Asn Ser Thr Tyr Ser Arg Leu Lys Thr
 85 90 95
 Glu Ser Tyr Asn Lys Ala Asp Val Ile Ile Ala Asp Pro Tyr Leu Lys
 100 105 110
 15 Tyr Gly Asp Asp Pro Tyr Thr Leu Gln Tyr Gly Gly Cys Ala Met Lys
 115 120 125
 Gly Arg Tyr Ile His Phe Thr Pro Asn Phe Leu Leu Asp Ser Ser Leu
 130 135 140
 20 Ile Lys Val Tyr Gly Glu Arg Gly Arg Val Leu Val His Glu Trp Ala
 145 150 155 160
 His Thr Ser Val Gly Cys Val Xaa Arg Ile Xaa Xaa Arg Arg Asn Leu
 165 170 175
 Phe Asp Val Ser Glu Asn Ala Arg Val Glu Pro Thr Arg Cys Ser Ala
 180 185 190
 25 Gly Val Thr Trp Xaa Thr Cys Ile Pro Lys Leu Gln Trp Lys Thr Val
 195 200 205
 Tyr Asp Lys Arg Met Pro Ser Met Met Val Ser Tyr Met Lys Leu Gly
 210 215 220
 30 Cys Gly Ile Gly Asn Gly Ser Ser Ile Lys Lys Arg Lys Asn Ser Ile
 225 230 235 240
 Met Tyr Met Gln Ser Leu Pro Ser Val Val Glu Ser Val Ile Lys Ile
 245 250 255
 Leu Ile Asn Ser Glu Val Gln Asn Met Arg Asn Arg
 260 265
 35

<210> 21
 <211> 192
 40 <212> PRT
 <213> Gallus gallus

<400> 21
 Met Gly Val Phe Arg Ser Leu Ile Phe Leu Leu Ser Phe Gln Leu Leu
 1 5 10 15
 His Val Ala Lys Gly Ser Met Val Lys Leu Asn Glu Ser Gly Tyr Glu
 20 25 30
 Gly Leu Val Val Ala Ile Asn Pro Ser Val Thr Glu Asp Ala Asn Ile
 35 40 45
 50 Ile Leu Asn Thr Lys Ala Met Ile Lys Asp Ala Ser Asn Tyr Leu Phe
 50 55 60
 Glu Ala Thr Lys His Arg Phe Phe Phe Lys Ser Val Lys Ile Ile Leu
 65 70 75 80
 Pro Lys Thr Trp Lys Lys Asn Ser Thr Tyr Ser Arg Leu Lys Thr Glu
 85 90 95
 55 Ser Tyr Asn Lys Ala Asp Val Ile Ile Ala Asp Pro Tyr Leu Lys Tyr
 100 105 110

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      Gly Asp Asp Pro Tyr Thr Leu Gln Tyr Gly Gly Cys Ala Met Lys Gly
            115                120                125
      Arg Tyr Ile His Phe Thr Pro Asn Phe Leu Leu Asp Ser Ser Leu Ile
            130                135                140
5    Lys Val Tyr Gly Glu Arg Gly Arg Val Phe Val His Glu Trp Ala His
      145                150                155                160
      Leu Arg Trp Gly Val Phe Asp Glu Tyr Asn Asn Asp Ala Pro Phe Tyr
            165                170                175
10   Val Ser Glu Asn Ala Arg Val Glu Pro Thr Arg Cys Ser Ala Gly Val
            180                185                190

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      <210> 22
      <211> 202
15   <212> PRT
      <213> Salmo salar

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      <400> 22
20   Val Leu Leu Leu Val Tyr Leu Ser Gly Ser Thr Phe Gly Ile Lys Leu
      1          5                10                15
      Thr Gly Asn Gly Tyr Thr Asp Ile Leu Ile Ala Ile Asn Pro Val Val
            20                25                30
      Pro Glu Asp Pro Val Leu Ile Thr Gln Ile Glu Glu Met Ile Lys Glu
            35                40                45
25   Ala Ser Arg His Leu Leu Asn Ala Thr Lys Lys His Leu Tyr Phe Lys
      50          55                60
      Glu Val Ala Ile Leu Val Pro Pro Asn Trp Asn Lys Gly Asn Tyr Ser
      65          70                75                80
      Lys Ala Lys Thr Glu Val Tyr Asn Lys Ala Asn Ile Ile Ile Asp Glu
30   Pro Asn Arg Leu His Gly Asp Gln Pro Tyr Thr Leu Gln Tyr Gly Glu
            85                90                95
      Cys Gly Ser Glu Gly Gln Tyr Ile His Leu Thr Pro Asp Phe Met Leu
            100               105               110
35   Asn Asp Asp Val Ser Lys Tyr Tyr Gly Pro Arg Gly Lys Val Phe Val
      130          135                140
      His Glu Trp Ala His Leu Arg Trp Gly Val Phe Asp Glu Tyr Asn Glu
      145          150                155                160
      Glu Lys Pro Phe Tyr Leu Ser Gly Ser Ile Ile Glu Ala Thr Arg Cys
40   Thr Ile Asn Ile Thr Gly Lys Tyr Ile His Lys Arg Asp Gln Lys Asp
            165                170                175
            180                185                190
      Cys Thr Thr Asp Pro Val Thr Gly Leu Tyr
            195                200

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45   <210> 23
      <211> 202
      <212> PRT
50   <213> Strongylocentrotus purpuratus
      <220>
      <221> MISC_FEATURE
      <222> (186)..(186)
      <223> any natural amino acid residue
55   <220>
      <221> MISC_FEATURE
      <222> (192)..(192)
      <223> any natural amino acid residue

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<400> 23
 Asp Val Pro Glu Asp Gln Thr Ile Ile Asp Asn Leu Ile Asp Ile Phe
 1 5 10 15
 5 Ser Ser Gly Ser Gly His Leu Phe Thr Ala Thr Arg Arg Arg Ala Tyr
 20 25 30
 Trp Arg Asn Ile Thr Ile Leu Ile Pro Lys Thr Trp Thr Pro Lys Pro
 35 40 45
 Glu Tyr Glu Pro Ala Arg Thr Glu Ser Phe Glu Thr Ala Asn Val Ile
 50 55 60
 10 Ile Asp Thr Ala Asn Pro Glu Trp Glu Asp Asn Pro Tyr Thr Leu Gln
 65 70 75 80
 Leu Gly Gly Cys Gly Val His Gly Glu Tyr Ile His Leu Thr Pro Ser
 85 90 95
 15 Tyr Ile Thr Asp Arg Ala Asn Ser Glu Tyr Ile Trp Gly Ser Met Gly
 100 105 110
 Lys Leu Leu Ile His Glu Trp Gly His Leu Arg Trp Gly Leu Phe Asp
 115 120 125
 Glu Tyr His Thr Asp Asp Asp Gly Val Gln Lys Phe Tyr Ala Asp Ser
 130 135 140
 20 Arg Gly Glu Ile Val Ala Thr Arg Cys Thr Asp Gln Leu Asn Gly Glu
 145 150 155 160
 Ala Leu Asn Ile Asn Thr Phe Ala Pro Cys Gln Arg Asp Arg Asp Thr
 165 170 175
 25 Gly Leu Tyr Glu Asp Asp Cys Phe Tyr Xaa Pro Asp Leu Glu Gly Xaa
 180 185 190
 Thr Ser Pro Gly Ser Ile Met Tyr Ala Gln
 195 200

30

<210> 24
 <211> 192
 <212> PRT
 <213> Strongylocentrotus purpuratus

35

<400> 24
 Gly Arg Ile Leu Met Ser Val Val Val Cys Cys Leu Val Leu Phe Ser
 1 5 10 15
 Gly Val Ser Gly Ser Asp Leu Arg Asn Ser Ile Thr Ile Gln Asp Gly
 20 25 30
 40 Gly Tyr Glu Asn Val Leu Ile Ala Ile Asn Lys Asp Val Pro Glu Asp
 35 40 45
 Gln Thr Ile Ile Asp Asn Leu Ile Asp Ile Phe Ser Ser Gly Ser Gly
 50 55 60
 45 His Leu Phe Thr Ala Thr Arg Arg Arg Ala Tyr Trp Arg Asn Ile Thr
 65 70 75 80
 Ile Leu Ile Pro Lys Thr Trp Thr Pro Lys Pro Glu Tyr Glu Pro Ala
 85 90 95
 Arg Thr Glu Ser Phe Glu Thr Ala Asn Val Ile Ile Asp Thr Ala Asn
 100 105 110
 50 Pro Glu Trp Glu Asp Asn Pro Tyr Thr Leu Gln Leu Gly Cys Gly
 115 120 125
 Val His Gly Glu Tyr Ile His Leu Thr Pro Ser Tyr Ile Thr Asp Arg
 130 135 140
 55 Ala Asn Ser Glu Tyr Ile Trp Gly Ser Met Gly Lys Leu Leu Ile His
 145 150 155 160
 Glu Trp Ser His Leu Arg Trp Gly Leu Phe Asp Glu Tyr His Thr Asp
 165 170 175

Asp Asp Gly Val Gln Lys Phe Tyr Ala Asp Ser Arg Gly Val Arg Ser
 180 185 190

5 <210> 25
 <211> 131
 <212> PRT
 <213> Strongylocentrotus purpuratus

10 <400> 25
 Thr Ile Leu Leu Leu Glu Ile Phe Leu Val Glu Val Val Thr Gly Gln
 1 5 10 15
 Lys Asn Thr Ile Asn Leu Asn Asn Gly Ala Tyr Ser Asn Leu Leu Ile
 20 25 30
 15 Ala Ile Asp Lys Asn Val Ala Glu Asp Leu Asn Ile Ile Asp Asn Ile
 35 40 45
 Lys Thr Met Phe Thr Ser Ser Ser Glu Arg Leu Tyr Leu Ala Ser Lys
 50 55 60
 Gln His Val Tyr Trp Lys His Ile Lys Ile Leu Val Pro Asn Thr Trp
 65 70 75 80
 20 Ser Ile Gln Ser Gly Tyr Gln Phe Ser Arg Thr Glu Thr Leu Glu Ser
 85 90 95
 Ala Asn Ile Ile Leu His Asn Phe His Asp Asp Glu Pro Phe Val Asp
 100 105 110
 25 Asn Leu Ala Gly Cys Gly Lys Glu Gly Thr Leu Met His Met Thr Pro
 115 120 125
 Gly Tyr Ile
 130

30 <210> 26
 <211> 203
 <212> PRT
 <213> Xenopus tropicalis

35 <400> 26
 Ala Ser Ser Tyr Leu Phe Gln Ala Thr Lys Lys Arg Leu Tyr Ile Arg
 1 5 10 15
 Ser Ala Lys Ile Leu Ile Pro Asn Thr Trp Ala Thr Asn Ser Ser Tyr
 20 25 30
 40 Gly Arg Pro Lys Leu Glu Ser Tyr Asp Lys Ala Asp Val Ile Val Ala
 35 40 45
 Pro Pro Phe Val Gln Gly Asp Asp Pro Tyr Thr Leu Gln Phe Gly Gly
 50 55 60
 45 Cys Gly Glu Lys Gly Lys Tyr Ile His Phe Thr Pro Asn Phe Leu Val
 65 70 75 80
 Asn Asp Glu Lys Met Leu Pro Ile Tyr Gly Pro Arg Gly Arg Val Phe
 85 90 95
 Val His Glu Trp Ala His Phe Arg Trp Gly Val Phe Asp Glu Tyr Asn
 100 105 110
 50 Tyr Asn Arg Pro Tyr Tyr Phe Ser Glu Asn Arg Lys Val Glu Ala Thr
 115 120 125
 Arg Cys Pro Leu Lys Leu Lys Gly Leu Asn Leu Ile Asp Val Cys Gln
 130 135 140
 55 Arg Gly Val Cys Asn Leu Glu Pro Cys Glu Tyr Asp Lys Asn Thr Gly
 145 150 155 160
 Leu Tyr Glu Glu Asp Cys Lys Phe Tyr Pro Asp Arg Asp Ile Leu Val
 165 170 175

Glu Glu Ser Val Met Tyr Ala Gln Met Phe Glu Pro Val His Ala Phe
 180 185 190
 Cys Asp Ser Ser Ser His Asn Ser Glu Ala Pro
 5 195 200

<210> 27
 <211> 108
 10 <212> PRT
 <213> Xenopus laevis

<400> 27
 15 Asp Ser Leu Val Gln Leu Lys Asn Asn Gly Tyr Glu Asp Ile Ile Ile
 1 5 10 15
 Ala Val Asn Pro Glu Val Pro Glu Asp Gly Lys Ile Ile Glu Gln Ile
 20 25 30
 Lys Lys Met Leu Thr Asp Ala Ser Ser Tyr Leu Phe Gln Ala Thr Lys
 35 40 45
 20 Lys Arg Ile Tyr Ile Arg Ser Ala Lys Ile Leu Ile Pro Asn Ser Trp
 50 55 60
 Thr Ser Asn Ser Ser Tyr Gly Arg Pro Lys Leu Glu Ser Tyr Asp Lys
 65 70 75 80
 Ala Asp Val Ile Val Ala Ser Pro Phe Ile His Gly Asp Asp Pro Tyr
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 25 Thr Leu Pro Val Trp Arg Leu Trp Arg Lys Gly Lys
 100 105

30 <210> 28
 <211> 124
 <212> PRT
 <213> Xenopus laevis

35 <400> 28
 Ala Thr Arg Cys Pro Leu Lys Met Gln Gly Ser Tyr Leu Ile Glu Val
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 Cys Gln Arg Gly Ile Cys Asn Leu Glu Ala Cys Glu Tyr Asp Glu Asn
 20 25 30
 40 Thr Gly Leu Tyr Glu Glu Asp Cys Lys Phe Tyr Pro Lys Met Asp Ser
 35 40 45
 Asn Val Glu Glu Ser Val Met Tyr Ala Gln Met Met Glu Pro Val His
 50 55 60
 Ala Phe Cys Asn Ser Ser Ser His Asn Ser Glu Ala Pro Asn Gln Gln
 65 70 75 80
 45 Asn Arg Leu Cys Ser Gln Gln Ser Thr Trp Asp Val Ile Ser Lys Ser
 85 90 95
 Ser Asp Ile Gln Ser Ser Pro Pro Leu Met Asp Ser Asn Ile Pro Ala
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 50 Pro Val Val Ser Leu Leu Gln Tyr Lys Asp Arg Val
 115 120

<210> 29
 <211> 96
 <212> PRT
 <213> *Xenopus tropicalis*

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<400> 29

Asp Ser Leu Val Gln Leu Lys Asn Asn Gly Tyr Glu Asp Ile Ile Ile
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 Ala Val Asn Pro Gln Val Pro Glu Asp Gly Lys Ile Ile Glu Asn Ile
 10 20 25 30
 Lys Lys Met Leu Thr Asp Ala Ser Ser Tyr Leu Phe Gln Ala Thr Lys
 35 40 45
 Lys Arg Leu Tyr Ile Arg Ser Ala Lys Ile Leu Ile Pro Asn Thr Trp
 50 55 60
 15 Ala Thr Asn Ser Ser Tyr Gly Arg Pro Lys Leu Glu Ser Tyr Asp Lys
 65 70 75 80
 Ala Asp Val Ile Val Ala Pro Pro Phe Val Gln Arg Asp Asp Pro Tyr
 85 90 95

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<210> 30
 <211> 201
 <212> PRT
 <213> *Rattus norvegicus*

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<400> 30

Gly Arg Asp Glu Pro Tyr Thr Arg Gln Phe Thr Lys Cys Gly Lys Lys
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 Ala Glu Tyr Ile His Phe Thr Pro Asp Phe Val Leu Gly Arg Lys Gln
 30 20 25 30
 Lys Glu Tyr Gly Asp Ser Gly Arg Leu Leu Val His Glu Trp Ala His
 35 35 40 45
 Leu Arg Trp Gly Val Phe Asp Glu Tyr Asn Glu Asp Gln Pro Phe Tyr
 50 55 60
 35 Ser Ala Ser Ser Lys Lys Ile Glu Ala Thr Arg His Val Leu Thr Pro
 65 70 75 80
 Lys Cys Ser Thr Gly Ile Lys Gly Met Asn Lys Ala Gln Val Cys Gln
 85 90 95
 Gly Gly Ser Cys Ile Thr Arg Asn Cys Arg Arg Asn Ser Thr Thr Gln
 40 100 105 110
 Leu Tyr Glu Lys Asp Cys Gln Phe Phe Pro Asp Lys Val Gln Thr Glu
 115 120 125
 Lys Ser Ser Ile Met Phe Met Gln Ser Ile Asp Ser Val Thr Glu Phe
 130 135 140
 45 Cys Lys Lys Glu Asn His Asn Arg Glu Ala Pro Thr Leu His Asn Gln
 145 150 155 160
 Lys Cys Asp Tyr Arg Ser Thr Trp Glu Val Ile Ser Asn Ser Glu Asp
 165 170 175
 Phe Lys Asn Ser Thr Pro Met Glu Met Pro Pro Ser Pro Pro Phe Phe
 50 180 185 190
 Ser Leu Leu Arg Ile Ser Glu Arg Ile
 195 200

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<210> 31
 <211> 333
 <212> PRT
 <213> Rattus norvegicus

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<400> 31
 Val Lys Ser Ser Lys Val His Leu Asn Asn Asn Gly Tyr Glu Gly Val
 1 5 10 15
 Val Ile Ala Ile Asn Pro Ser Val Pro Glu Asp Glu Arg Leu Ile Pro
 20 25 30
 Ser Leu Lys Ala Lys Cys Leu Gly Arg Ser Gly Val Leu Ser Gly Ala
 35 40 45
 Glu Asn His Glu Leu Ser Ser Arg Ala Leu Cys Cys Trp Gly Cys Phe
 50 55 60
 Gly Phe Leu Ala Val Pro His Asn Ala Ala Tyr Thr Ala Asp His Lys
 65 70 75 80
 Gly Asn Gln Ala Asp Val Ile Val Ala Asp Pro His Leu Lys Tyr Gly
 85 90 95
 Asp Asp Pro Tyr Thr Leu Gln Tyr Gly Gln Cys Gly Asp Arg Gly Gln
 100 105 110
 Tyr Ile His Phe Thr Pro Asn Phe Leu Leu Ile Asp Asn Leu Ile Ile
 115 120 125
 Tyr Gly Pro Arg Gly Arg Val Phe Val His Glu Trp Ala His Leu Arg
 130 135 140
 Trp Gly Val Phe Asp Glu Tyr Asn Lys Glu Arg Pro Phe Tyr Leu Ser
 145 150 155 160
 Arg Lys Asn Val Val Glu Ala Thr Arg Cys Ser Thr Asp Ile Thr Gly
 165 170 175
 Thr Asn Val Val His Glu Cys Gln Gly Gly Ser Cys Val Thr Arg Lys
 180 185 190
 Cys Arg Arg Asp Ser Lys Thr Gly Leu Pro Glu Pro Lys Cys Thr Phe
 195 200 205
 Ile Pro Asn Lys Ser Gln Thr Ala Arg Ala Ser Ile Met Phe Leu Gln
 210 215 220
 Ser Leu Asp Ser Arg Arg Met Ile Phe Tyr Gly Gly Ile Lys Lys Cys
 225 230 235 240
 Val Leu Asn Lys Arg Gln Glu Met Gly Leu Asn Leu Gln Ser Tyr Lys
 245 250 255
 Ala Arg Val Leu Gly Phe Ser Pro Leu Tyr Phe Gly Arg Met Val Val
 260 265 270
 Glu Phe Cys Thr Glu Lys Thr His Asn Thr Glu Ala Pro Asn Leu Gln
 275 280 285
 Asn Lys Ile Cys Asn Gly Arg Ser Thr Trp Asp Val Ile Lys Glu Ser
 290 295 300
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 305 310 315 320
 Pro Pro Thr Phe Ser Leu Leu Lys Ser Arg Gln Arg Val
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<210> 32
 <211> 335
 <212> PRT
 <213> Rattus norvegicus

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 Gly Val Val Ile Ala Ile Asn Pro Ser Val Pro Glu Asp Glu Arg Leu
 35 40 45
 5 Ile Pro Ser Leu Lys Glu Met Val Thr Gln Ala Ser Thr Tyr Leu Phe
 50 55 60
 Glu Ala Ser Gln Gly Arg Phe Tyr Phe Arg Asn Val Ser Ile Leu Val
 65 70 75 80
 10 Pro Met Thr Trp Lys Ser Lys Ser Glu Tyr Leu Met Pro Lys Arg Glu
 85 90 95
 Ser Tyr Asp Lys Ala Asp Val Ile Val Ala Asn Ser His Leu Lys Tyr
 100 105 110
 Gly Asp Asn Pro Tyr Thr Leu Gln Tyr Gly Gln Cys Gly Asp Arg Gly
 115 120 125
 15 Arg Tyr Ile His Phe Thr Pro Asn Phe Leu Leu Thr Asp Asn Val Arg
 130 135 140
 Asn Tyr Gly Pro Arg Gly Arg Val Phe Val His Glu Trp Ala His Leu
 145 150 155 160
 Arg Trp Gly Val Phe Asp Glu Tyr Asn Glu Asp Arg Pro Phe Tyr Ile
 165 170 175
 20 Ser Gly Lys Asn Thr Ile Glu Val Thr Arg Tyr Leu Cys Glu Leu Ser
 180 185 190
 Asp Ser Thr Thr Ser Tyr Leu Arg Val Phe Ser Arg Pro Tyr Arg Ala
 195 200 205
 25 Val Gln Val Thr Gly Cys Ser Thr Asp Ile Lys Gly Ser Lys Ala Val
 210 215 220
 His Glu Arg Gln Arg Gly Ser Asp Val Thr Arg Leu Cys Arg Trp Asp
 225 230 235 240
 Ser Arg Thr Gly Leu Tyr Glu Pro Lys Cys Lys Phe Phe Pro Asp Lys
 245 250 255
 30 Ile Gln Thr Ala Arg Ala Ser Ile Met Phe Met Gln Asn Leu Asn Ser
 260 265 270
 Val Val Glu Phe Cys Thr Glu Lys Thr His Asn Thr Glu Ala Pro Asn
 275 280 285
 35 Leu Gln Asn Lys Ile Cys Asn Gly Arg Ser Thr Trp Asp Val Ile Lys
 290 295 300
 Glu Ser Ala Asp Phe Gln Gln Ala Pro Pro Met Arg Gly Thr Glu Ala
 305 310 315 320
 Pro Pro Pro Pro Thr Phe Ser Leu Leu Lys Ser Arg Gln Arg Val
 325 330 335
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 <210> 33
 <211> 307
 45 <212> PRT
 <213> Rattus norvegicus

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 Glu Gly Ile Val Ile Ala Ile Asp His Asp Val Pro Glu Asp Glu Ala
 35 40 45
 55 Leu Ile Gln Arg Ile Lys Asp Met Val Thr Gln Ala Ser Pro Tyr Leu
 50 55 60
 Phe Glu Ala Thr Gly Lys Arg Phe Tyr Phe Lys Asn Val Ala Ile Leu
 65 70 75 80

Ile Pro Glu Asn Trp Asn Thr Lys Pro Glu Tyr Lys Arg Pro Lys Leu
 85 90 95
 Glu Thr Leu Lys Asn Ala Asp Val Leu Val Ser Thr Met Ser Pro Ile
 100 105 110
 5 Gly Asn Asp Glu Pro Tyr Thr Glu His Ile Gly Ala Cys Gly Glu Arg
 115 120 125
 Gly Ile Arg Ile His Leu Thr Pro Asp Phe Leu Ala Gly Lys Lys Gln
 130 135 140
 10 Thr Glu Tyr Gly Pro Gln Asp Arg Thr Phe Val His Glu Trp Ala His
 145 150 155 160
 Phe Arg Trp Gly Val Phe Asp Glu Tyr Asn Asn Asn Glu Lys Phe Tyr
 165 170 175
 Leu Ser Asn Gly Lys Pro Gln Ala Val Arg Cys Ser Ala Thr Ile Thr
 180 185 190
 15 Gly Lys His Val Val Arg Arg Cys Gln Gly Gly Ser Cys Val Thr Asn
 195 200 205
 Gly Lys Cys Val Ile Asp Arg Val Thr Gly Leu Tyr Lys Asp Asn Cys
 210 215 220
 Val Phe Ile Pro Asp Lys Asn Gln Arg Glu Lys Ala Ser Ile Met Phe
 225 230 235 240
 20 Asn Gln Asn Ile Asn Ser Val Val Glu Phe Cys Thr Glu Lys Asn His
 245 250 255
 Asn Lys Glu Ala Pro Asn Ala Gln Asn Gln Arg Cys Asn Leu Arg Ser
 260 265 270
 25 Thr Trp Glu Val Ile Gln Glu Ser Glu Asp Phe Lys Gln Thr Thr Pro
 275 280 285
 Met Thr Ala Gln Pro Pro Ala Pro Thr Phe Ser Leu Leu Gln Thr Arg
 290 295 300
 Gln Arg Ile
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 <210> 34
 <211> 279
 35 <212> PRT
 <213> Rattus norvegicus

 <400> 34
 Leu Lys Leu Lys Glu Asn Gly Tyr Asp Gly Leu Leu Val Ala Ile Asn
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 40 Pro Arg Val Pro Glu Asp Leu Lys Leu Ile Arg Asn Ile Gln Glu Met
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 Ile Thr Glu Ala Ser Phe Tyr Leu Phe Asn Ala Thr Lys Arg Arg Val
 35 40 45
 45 Phe Phe Arg Ser Val Gln Ile Leu Ile Pro Ala Thr Trp Thr Ala His
 50 55 60
 Asn Tyr Ser Arg Val Lys Gln Glu Ser Phe Asp Lys Ala Asn Val Leu
 65 70 75 80
 Val Thr Glu Gln Asn Gly Val Pro Gly Glu Asp Pro Tyr Thr Leu Gln
 85 90 95
 50 His Arg Gly Cys Gly Gln Glu Gly Lys Tyr Ile His Phe Thr Pro Asn
 100 105 110
 Phe Leu Leu Asn Asp Glu Leu Ala Gly Tyr Gly Ser Arg Gly Arg
 115 120 125
 55 Val Phe Val His Glu Trp Ala His Leu Arg Trp Gly Val Phe Asp Glu
 130 135 140
 Tyr Asn Ser Asp Lys Pro Phe Tyr Val Asn Gly Arg Asn Glu Ile Gln
 145 150 155 160

Val Thr Arg Cys Ser Ser Asp Ile Thr Gly Val Phe Val Cys Glu Lys
 165 170 175
 Gly Leu Cys Pro His Glu Asp Cys Ile Ile Ser Lys Leu Phe Arg Glu
 180 185 190
 5 Gly Cys Thr Phe Leu Tyr Asn Ser Thr Gln Ser Ala Thr Gly Ser Ile
 195 200 205
 Met Phe Met Gln Ser Leu Pro Ser Val Val Glu Phe Cys Asn Glu Gly
 210 215 220
 10 Thr His Asn Arg Glu Ala Pro Asn Leu Gln Asn Arg Val Cys Ser Leu
 225 230 235 240
 Arg Ser Thr Trp Asp Val Ile Thr Gly Ser Ser Asp Leu Asn His Ser
 245 250 255
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 260 265 270
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 20 <211> 246
 <212> PRT
 <213> Rattus norvegicus

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 30 Asp Ile Ile Ile Ala Ile Asp Pro Ala Val Ser Glu Asp Val Thr Ile
 35 40 45
 Ile Asp Gln Ile Lys Asp Met Val Thr Lys Ala Ser Ala Tyr Leu Phe
 50 55 60
 Glu Ala Thr Glu Lys Arg Phe Phe Phe Lys Asn Val Ser Ile Leu Ile
 65 70 75 80
 35 Pro Glu Asn Trp Thr Asn Ser Asp Gln Tyr Arg Arg Pro Lys Gln Glu
 85 90 95
 Ser Tyr Lys His Ala Asp Ile Lys Val Ala Pro Pro Ala Leu Gln Gly
 100 105 110
 40 Arg Asp Glu Pro Tyr Thr Arg Gln Phe Thr Lys Cys Gly Lys Lys Ala
 115 120 125
 Glu Tyr Ile His Phe Thr Pro Asp Phe Val Leu Gly Arg Lys Gln Lys
 130 135 140
 Glu Tyr Gly Asp Ser Gly Arg Leu Leu Val His Glu Trp Ala His Leu
 145 150 155 160
 45 Arg Trp Gly Val Phe Asp Glu Tyr Asn Glu Asp Gln Pro Phe Tyr Ser
 165 170 175
 Ala Ser Ser Lys Lys Ile Glu Ala Thr Arg Cys Ser Thr Gly Ile Lys
 180 185 190
 Gly Met Asn Lys Ala Gln Val Cys Gln Gly Gly Ser Cys Ile Thr Arg
 195 200 205
 50 Asn Cys Arg Arg Asn Ser Thr Thr Gln Leu Tyr Glu Lys Asp Cys Gln
 210 215 220
 Phe Phe Pro Asp Lys Val Gln Thr Glu Lys Ser Ser Ile Met Phe Met
 225 230 235 240
 55 Gln Ser Ile Asp Ser Val
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<210> 36
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 <212> PRT
 <213> Rattus norvegicus

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 Gly Val Val Ile Ala Ile Asn Pro Ser Val Pro Glu Asp Glu Arg Leu
 35 40 45
 Ile Pro Ser Leu Lys Glu Met Val Thr Gln Ala Ser Thr Tyr Leu Phe
 50 55 60
 Glu Ala Ser Gln Gly Arg Phe Tyr Phe Arg Asn Val Ser Ile Leu Val
 65 70 75 80
 Pro Met Thr Trp Lys Ser Lys Ser Glu Tyr Leu Met Pro Lys Arg Glu
 85 90 95
 Ser Tyr Asp Lys Ala Asp Val Ile Val Ala Asn Ser His Leu Lys Tyr
 100 105 110
 Gly Asp Asn Pro Tyr Thr Leu Gln Tyr Gly Gln Cys Gly Asp Arg Gly
 115 120 125
 Arg Tyr Ile His Phe Thr Pro Asn Phe Leu Leu Thr Asp Asn Val Arg
 130 135 140
 Asn Tyr Gly Pro Arg Gly Arg Val Phe Val His Glu Trp Ala His Leu
 145 150 155 160
 Arg Trp Gly Val Phe Asp Glu Tyr Asn Glu Asp Arg Pro Phe Tyr Ile
 165 170 175
 Ser Gly Lys Asn Thr Ile Glu Val Thr Arg Cys Ser Thr Asp Ile Lys
 180 185 190
 Gly Ser Lys Ala Val His Glu Arg Gln Arg Gly Ser Asp Val Thr Arg
 195 200 205
 Leu Cys Arg Trp Asp Ser Arg Thr Gly Leu Tyr Glu Pro Lys Cys Lys
 210 215 220
 Phe Phe Pro Asp Lys Ile Gln Thr Ala Arg Ala Ser Ile Met Phe Met
 225 230 235 240
 Gln Asn Leu Asn Ser Val Val Glu Phe Cys Thr Glu Lys Thr His Asn
 245 250 255
 Thr Glu Ala Pro Asn Leu Gln Asn Lys Ile Cys Asn Gly Arg Ser Thr
 260 265 270
 Trp Asp Val Ile Lys Glu Ser Ala Asp Phe Gln Gln Ala Pro Pro Met
 275 280 285
 Arg Gly Thr Glu Ala Pro Pro Pro Pro Thr Phe Ser Leu Leu Lys Ser
 290 295 300
 Arg Gln Arg Val
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<210> 37
 <211> 162
 <212> PRT
 <213> Homo sapiens

<400> 37
 Asp Pro Asn Val Pro Glu Asp Glu Thr Leu Ile Gln Gln Ile Lys Asp
 1 5 10 15
 Met Val Thr Gln Ala Ser Leu Tyr Leu Phe Glu Ala Thr Gly Lys Arg
 20 25 30

Phe Tyr Phe Lys Asn Val Ala Ile Leu Ile Pro Glu Thr Trp Lys Thr
 35 40 45
 Lys Ala Asp Tyr Val Arg Pro Lys Leu Glu Thr Tyr Lys Asn Ala Asp
 50 55 60
 5 Val Leu Val Ala Glu Ser Thr Pro Pro Gly Asn Asp Glu Pro Tyr Thr
 65 70 75 80
 Glu Gln Met Gly Asn Cys Gly Glu Lys Gly Glu Arg Ile His Leu Thr
 85 90 95
 Pro Asp Phe Ile Ala Gly Lys Lys Leu Ala Glu Tyr Gly Pro Gln Gly
 100 105 110
 10 Lys Ala Phe Val His Glu Trp Ala His Leu Arg Trp Gly Val Phe Asp
 115 120 125
 Glu Tyr Asn Asn Asp Glu Lys Phe Tyr Leu Ser Asn Gly Arg Ile Gln
 130 135 140
 15 Ala Val Arg Cys Ser Ala Gly Ile Thr Gly Thr Asn Val Val Lys Lys
 145 150 155 160
 Cys Gln

20 <210> 38
 <211> 31
 <212> DNA
 <213> Artificial Sequence
 25 <220>
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<400> 38
 atgtcgacca tatgattcaa caaataaagg a

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 <210> 39
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<400> 39
 40 atgcggcgcg tcactttcttt actacatttg tac

33

<210> 40
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 45 <212> DNA
 <213> Artificial Sequence
 <220>
 <223> synthetically generated oligonucleotide

<400> 40
 50 catatgtcac tcattcagct gaacaac

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<210> 41
 55 <211> 25
 <212> DNA
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<220>
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<400> 41
5 catatggaag atgaaacact cattc 25

<210> 42
<211> 32
10 <212> DNA
<213> Artificial Sequence
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<223> synthetically generated oligonucleotide

<400> 42
15 gcggccgctc acttctttac tacatttgta cc 32

<210> 43
20 <211> 30
<212> DNA
<213> Artificial Sequence
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<223> synthetically generated oligonucleotide

<400> 43
25 gcggccgctc acttggttgg agcttctttg 30

<210> 44
30 <211> 6
<212> PRT
<213> Artifical Sequence
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<221> MISC_FEATURE
35 <222> (1)..(1)
<223> (7-methoxy-coumarin-4-yl)acetyl or Mca
<220>

<221> MISC_FEATURE
40 <222> (6)..(6)
<223> (2,4-dinitrophenyl)-L-2,3-diaminopropionyl or Dpa

<400> 44
Xaa Lys Ala Met His Xaa
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CLAIMS

What we claim is:

- 5 1. A method for identifying a compound capable of modulating the hydrolase activity of a CLCA protein which method comprises:
 - (a) subjecting one or more test compounds to a screen comprising at least one protein selected from the group consisting of: a CLCA protein or a fragment thereof; a
homologue of a CLCA protein or a fragment thereof; and
 - 10 (b) measuring the hydrolase activity of the CLCA protein or homologue or fragment; and
 - (c) comparing the measured hydrolase activity with the hydrolase activity of the CLCA protein or homologue or fragment in the absence of the test compound.
- 15 2. A method as claimed in claim 1 wherein at least one of the proteins is selected from the group consisting of: a mammalian CLCA protein or a fragment thereof; a homologue of a mammalian CLCA protein or a fragment thereof.
3. A method as claimed in claim 2 wherein at least one of the proteins is selected from
20 the group consisting of: a human CLCA protein or a fragment thereof; a homologue of a human CLCA protein or a fragment thereof.
4. A method as claimed in claim 3 wherein at least one of the proteins is selected from
25 the group consisting of: hCLCA1 or a fragment thereof; a homologue of hCLCA1 or a fragment thereof.
5. A method as claimed in claim 1 wherein the CLCA protein or fragment thereof or the
homologue of a CLCA protein or fragment thereof is present as a fusion protein.
30

6. A method to design a compound capable of modulating CLCA hydrolase activity which comprises molecular modelling based on the interaction of a potential modulator with a hydrolase domain of a CLCA protein or homologue or fragment of either, wherein the three-dimensional structure of the hydrolase domain is defined by the set of atomic coordinates shown in Table 1.
7. A method to design a compound capable of modulating CLCA hydrolase activity which comprises molecular modelling based on the interaction of a potential modulator with the active site of a hydrolase domain of a CLCA protein or homologue or fragment of either, wherein the three-dimensional structure of the hydrolase domain is defined by the set of atomic coordinates shown in Table 1 and the active site comprises the amino acid residues within 15Å of atom Zn-1300 in the set of atomic coordinates shown in Table 1.
8. A method for *in silico* screening for a compound capable of modulating CLCA hydrolase activity which comprises
- b) searching a structural database of compounds; and
 - b) selecting a compound structure that may interact with a hydrolase domain of a CLCA protein or homologue or fragment of either, wherein the three-dimensional structure of the hydrolase domain is defined by the set of atomic coordinates shown in Table 1.
9. A method for *in silico* screening for a compound capable of modulating CLCA hydrolase activity which comprises
- c) searching a structural database of compounds; and
 - b) selecting a compound structure that may interact with the active site of a hydrolase domain of a CLCA protein or homologue or fragment of either, wherein the three-dimensional structure of the hydrolase domain is defined by the set of atomic coordinates shown in Table 1 and the active site comprises the amino acid

residues within 15Å of atom Zn-1300 in the set of atomic coordinates shown in Table 1.

- 5 10. A method for designing an antibody capable of modulating the hydrolase activity of a CLCA protein which method comprises using the three-dimensional structure of a CLCA hydrolase domain to identify suitable epitopes in the vicinity of the active site, wherein the three-dimensional structure of the hydrolase domain is defined by the set of atomic coordinates shown in Table 1 and the active site comprises the amino acid residues within 15Å of atom Zn-1300 in the set of atomic coordinates shown in Table
- 10 1.
11. A method as claimed in claim 10 wherein the epitopes include only surface residues within 15Å of atom Zn-1300 in the set of atomic coordinates shown in Table 1.

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A B S T R A C T**METHODS**

- 5 Methods for identifying compounds capable of modulating the hydrolase activity of a CLCA protein include screening and computer modelling methods. The compounds, including antibodies, may be useful as therapeutic agents to treat a variety of diseases.